Diabetes Mellitus Testing - CAM 133

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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.[1] 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 two hours, typically in the setting of pregnancy.[2] In an asymptomatic individual, FPG ≥ 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, individuals with percentages 5.7 to <6.5% are at highest risk. Additionally, there is a continuum of increasing risk amongst individuals with A1c levels <6.5%.[3] 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.[4]

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 twelve weeks.5 The measurement of hemoglobin A1c is recommended for diabetes management, including screening, diagnosis, and monitoring for diabetes and prediabetes.

Terms such as male and female are used when necessary to refer to sex assigned at birth.

Policy

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. For individuals with acute or persistent classic symptoms of diabetes mellitus, measurement of plasma glucose is considered **MEDICALLY NECESSARY**.
2. For individuals with a diagnosis of either Type 1 or Type 2 diabetes mellitus, measurement of hemoglobin A1c is 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.
    e. Quarterly for individuals who are pregnant.
3. For prediabetic individuals, annual screening for type 2 diabetes with a fasting plasma glucose test or measurement of hemoglobin A1c is considered **MEDICALLY NECESSARY**.
4. For asymptomatic individuals who are 35 years of age or older and who have no risk factors for diabetes, screening for prediabetes or type 2 diabetes once every three years with a fasting plasma glucose test is considered **MEDICALLY NECESSARY**.
5. For 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 is 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 1) 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 with metabolic dysfunction-associated steatotic liver disease (MASLD).
    j. For individuals who were previously diagnosed with gestational diabetes mellitus (GDM).
6. For individuals who are positive for HIV, screening for diabetes and prediabetes with a fasting plasma glucose test is 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.
7. 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 is considered **MEDICALLY NECESSARY**.
8. For overweight or obese individuals less than 18 years of age, diabetes screening once every three years with a fasting plasma glucose test, an OGTT, or measurement of hemoglobin A1c is 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 1).
    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).
9. For pregnant individuals, a fasting plasma glucose test or an OGTT up to once per month during pregnancy is considered **MEDICALLY NECESSARY**.
10. For individuals diagnosed with GDM during pregnancy, an OGTT is 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 or prediabetes.
11. For all other situations not addressed above, fasting plasma glucose testing at a wellness visit with no abnormal findings is considered **NOT MEDICALLY NECESSARY**.

12. For all other situations not previously described (see Note 2), measurement of hemoglobin A1c is considered **NOT MEDICALLY NECESSARY**.

NOTES:

Note 1: 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 2: Measurement of hemoglobin A1c should not be performed in any of the following situations:

1. To test for diabetes in individuals presenting with acute or persistent classic symptoms of diabetes mellitus.
2. In pregnant individuals without an established diagnosis of diabetes or prediabetes.
3. To screen for diabetes in individuals diagnosed with cystic fibrosis.
4. In conjunction with measurement of fructosamine.
5. In individuals with a condition associated with increased red blood cell turnover (e.g., individuals with sickle cell disease or who are HIV positive, individuals receiving hemodialysis or erythropoietin therapy or who have had recent blood loss or a transfusion).

Table of Terminology

Term	Definition
1,5AG	1,5-Anhydroglucitol
2-h PG	2-h plasma glucose
A1c	Glycated hemoglobin
AACE	American Association of Clinical Endocrinologists
AAFP	American Academy of Family Physicians
ACE	American College of Endocrinology
ACP	American College of Physicians
ADA	American Diabetes Association
ALT	Alanine transaminase
aRR	Adjusted risk ratios
ARV	Antiretroviral
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transferase
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
CAP	College of American Pathologists
CF	Cystic fibrosis
CFPD	Cystic fibrosis-related prediabetes
CFRD	Cystic fibrosis-related diabetes
CGM	Continuous glucose monitoring
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CLIA	Clinical Laboratory Improvement Amendment
CMS	Centers For Medicare and Medicaid Services
COVID-19	Coronavirus 19
CV	Coefficient of variation
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
ELF	Enhanced liver fibrosis
ELs	Evidence levels
FA	Fructosamine
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 index
FPG	Fasting plasma glucose
GA	Glycated albumin
GAD65	Glutamic acid decarboxylase 65
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
GGT	Gamma-glutamyl transferase
GLP-1	Glucagon-like peptide-1
GPP	Good practice point
HbA1c	Hemoglobin A1C/Glycated hemoglobin
HDL	High-density lipoprotein
HIV/AIDS	Human immunodeficiency virus, acquired immunodeficiency syndrome
HPLC	High-performance liquid chromatography
HR	Hospitalization rate

HRH	Hypoglycemia-related hospitalization
IA-2	Islet antigen 2
IFCC	International Federation of Clinical Chemistry
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
ISPAD	International Society for Pediatric and Adolescent Diabetes
KDIGO	Kidney Disease: Improving Global Outcomes Diabetes Working Group
LCD	Local coverage determine
LDTs	Laboratory-developed tests
MACE	Major adverse cardiovascular events
MASLD	Metabolic dysfunction-associated steatotic liver disease
MODY	Maturity-onset diabetes of the young
NACB	National Academy of Clinical Biochemistry
NAFLD	Nonalcoholic fatty liver disease
NCD	National coverage determination
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OGTT	Oral glucose tolerance test
OR	Odds ratio
OSA	Obstructive sleep apnea
PAD	Peripheral artery disease
PCOS	Polycystic ovary syndrome
PG	Plasma glucose
POC	Point-of-care
ROC-AUC	Receiver operative characteristic, area under the curve
SES	Socioeconomic status
SGLT2	Sodium-glucose cotransporter-2
SMBG	Self-monitoring of blood glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TIA	Transient ischemic attack
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization
ZnT8	Zinc transporter 8

Rationale

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

- Prevalence: In 2021, 38.4 million Americans, or 11.6% 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 38.4 million, 29.7 million were diagnosed, and 8.7 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: 1.2 million Americans are diagnosed with diabetes every year.
- Prediabetes: In 2021, 97.6 million Americans aged eighteen and older had prediabetes.
- Deaths: Diabetes remains the 8th leading cause of death in the United States in 2021, with 103,294 death certificates listing it as the underlying cause of death, and a total of 399.401 death certificates listing diabetes as a cause of death.
- Total economic cost of diabetes care in the United States: $413 billion in 2022.[6,7]

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)”[8] 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.[3]

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 twelve 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 ninety 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."[5]

The HbA1c assay provides information about the degree of long-term glucose control,[9] and has been recommended for the diagnosis and monitoring of diabetes.[8,10] Various methods of HbA1c measurement include chromatography based HPLC assay, boronate affinity, antibody-based immunoassay, and enzyme based enzymatic assay.[11] Long-term blood sugar control has been associated with decreased risk of retinopathy, nephropathy, neuropathy, and cardiovascular disease, peripheral arterial, cerebrovascular disease,[12] and myocardial fibrosis in adults with diabetes.[13] Higher HbA1c variability has been associated with higher all-cause mortality in patients with Type 2 Diabetes.[14]

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 OGTT, but HbA1c, FPG, or OGTTs with their respective positive results can be used in diagnosing diabetes mellitus in nonpregnant individuals as well. To diagnose diabetes in asymptomatic individuals, a FPG 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/DI.[3,4]

Traditionally, the diagnosis of diabetes was predicated on plasma glucose levels as well as symptom presentation. In 2010, the ADA endorsed as a "reliable retrospective marker of blood glucose control over the past 6-8 weeks." The advantages of HbA1c testing include increased convenience, increased stability and decreased variation in measurement. While the ADA 2023 guidelines gave precedence to FPG, the latest 2024 guideline addressed the vital importance of HbA1c for both diagnostic and screening purposes (for both diabetes and prediabetes care).

The ADA notes that there are areas where HbA1c is insufficient and plasma glucose levels are the preferred measurement: "In the presence of hemoglobin variants, pregnancy, glucose-6-phosphate dehydrogenase deficiency, and other conditions that might potentially interfere with accurate HbA1c measurements, plasma glucose levels are preferred. Furthermore, in situations where elevated blood glucose levels might not be consistently apparent, the diagnosis of diabetes necessitates two abnormal test results (HbA1c and plasma glucose) either simultaneously or at different time points. In such scenarios, alternative biomarkers such as fructosamine and glycated albumin emerge as viable options for monitoring glycemic status. Fructosamine reflects the total pool of glycated serum proteins, mainly albumin, reflecting glycemic trends over a span of two to four weeks—a relatively shorter duration compared to A1C. Although these biomarkers show a strong correlation and are associated with long-term complications based on epidemiological evidence, the empirical support for their application is not as robust as that for HbA1c."[15]

The OGTT can be more inconvenient and used in the setting to diagnose 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.[4,16]

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,[17] and a sound reference system is in place to ensure continuity and stability of the analytical validity of HbA1c measurement.[18] In contrast, plasma glucose concentration remains difficult to assay with consistent accuracy.[19] 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.[20,21] 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%).[22,23]

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 ranged from 0.7% to 4.0%" and "approximately 85% of laboratories are using methods with CVs <3% at all five HbA1c levels." The survey also noted the current pass limit was ±6%, but using a pass rate of 97.1% to 98.0% of labs passed.[24]

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 twelve percent of patients can be misclassified with respect to diabetes diagnosis due to laboratory instrument error in measuring glucose.[25] The New Hoorn Study analyzed the diagnostic properties of the A1c, using OGTT as the diagnostic criterion.[26] 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%.[22]

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.27 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.[28]

Cowie, et al. (2010) "examined prevalence's 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 prevalence's to those in earlier surveys and those using glucose criteria." 14,611 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 twenty years was 20.4 million, of which nineteen percent went undiagnosed based on A1c ≥ 6.5%. The authors then stated that the A1c criteria only diagnosed thirty percent of the undiagnosed diabetic group.[29]

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. Fourteen 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."[30]

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 zero or one of three years), medium (testing in two of three years), and high (testing in all three years).” Approximately 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.”[31]

The GOAL study 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 six months as targeted by the treating physician in adults with type 2 diabetes. In this study, 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 six and twelve months, respectively.”[32]

Mitsios, et al. (2018) evaluated the association between A1c and stroke risk. Twenty-nine 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 prediabetes range of 5.7%-6.5% was also not associated with first-ever stroke. The authors also observed that for every one percent 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.[33]

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, five-minute Apgar score less than seven, 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.[34]
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.”[35]

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.” FPG levels were not found to be associated with any pregnancy outcome.[36]

Arbiol-Roca, et al. (2021) studied the clinical utility of HbA1c testing as a biomarker for detecting GDM and as a screening test to avoid the use of the 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."[37]

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.”[38]

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 dysglycemia to minimize the burden of annual two-hour 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 zero, hour one, and hour two), 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.”[39]

By combining administrative datasets from the Veterans Health Administration and Medicare, Zhao, et al. (2021) evaluated the impact of hemoglobin A1c (A1c) variability—the CV, 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 342,059 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.[40]

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 ≥ nine percent remained a significant predictor for hospitalization." Given the evidence, the researchers urge "Paying special attention to patients with diabetes and an HbA1c ≥ nine 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.[41]

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, 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.[42]

Yang, et al. (2019) aimed to find the appropriate threshold for FPG 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 twelve to eighteen years." In using 4.75 mmol/L as the optimal threshold for children six to eleven years, the sensitivity was 65% and specificity was 51%. For the threshold of 5.19 mmol/L among children twelve to eighteen 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 individuals with term gestation and negative glucose challenge test (GCT) at 24 to 28 weeks. They recruited patients who had estimated fetal weights >90th percentile and a negative 50g GCT. From 170 individuals 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 twenty-four to twenty-eight 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.[44]

Bi, et al. (2024) engaged in a cross-sectional study of participants aged >20 years old who underwent physical examination at the local hospital from 2022 to 2023. A model was used to assess the dose-response relationship between liver enzymes and type 2 diabetes risk. Of the 14,100 participants, an analysis revealed a non-linear relationship between liver enzymes and type 2 diabetes risk (P non-linear < 0.001). Specifically, type 2 diabetes risk increased with rising ALT and GGT levels (range, <50 IU/L) and then leveled out when ALT and GGT levels were >50 IU/L. An elevated AST within a certain range (range, <35 IU/L) decreased the risk of type 2 diabetes, but a mildly elevated AST (>35 IU/L) showed as a risk factor for type 2 diabetes. In conclusion, liver enzymes were associated non-linearly with type 2 diabetes risk in different populations. Higher ALT and GGT levels were shown in this study to increase type 2 diabetes risk as well. In conclusion, additional attention should be paid to elevated liver enzymes and diabetes, but more work also needs to be done to assess association between elevation and T2D risk.

The American Diabetes Association (ADA)

The ADA publishes an extensive guideline encompassing the standards of medical care in diabetes. The 2024 recommendations state:

Classification and Diagnosis of Diabetes (Chapter [Ch] 2:[46]

- Criteria for testing for diabetes or prediabetes in asymptomatic adult:
  - Testing should be considered in overweight or obese (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian Americans) adults who have one or more of the following risk factors:
    - First-degree relative with diabetes
    - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
    - History of CVD
    - Hypertension (≥140/90 mmHg or on therapy for hypertension)
    - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
    - Individuals with polycystic ovary syndrome
    - Physical inactivity
    - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
  - People with prediabetes (A1c ≥5.7% [39 mmol/mol], IGT [impaired glucose tolerance], or IFG [impaired fasting glucose]) should be tested yearly.
  - People who were diagnosed with GDM should have lifelong testing at least every three years.
  - For all other patients, testing should begin at age thirty-five years.
  - If results are normal, testing should be repeated at a minimum of three-year intervals, with consideration of more frequent testing depending on initial results and risk status.
  - People with HIV, exposure to high-risk medicines, history of pancreatitis
- "Diabetes may be diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose (FPG) value, 2-h glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or random glucose value accompanied by classic hyperglycemic symptoms (e.g., polyuria, polydipsia, and unexplained weight loss) or hyperglycemic crises."

A1c

- "The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) as traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Grade **B**"
- "Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to U.S. Food and Drug Administration–approved devices at Clinical Laboratory Improvement Amendments (CLIA)–certified laboratories that perform testing of moderate complexity or higher by trained personnel. Grade **B**"
- "Marked discordance between A1C and repeat blood glucose values should raise the possibility of a problem or interference with either test. Grade **B**"
- "In conditions associated with an altered relationship between A1C and glycemia, such as some hemoglobin variants, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, plasma glucose criteria should be used to diagnose diabetes. Grade **B**"[8,46]

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 thirty-five years. Grade **B**"
- "If tests are normal, repeat screening recommended at a minimum of three-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 three days prior to testing. Grade **A**"
- "Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after ten 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**"
- "Consider screening people for prediabetes or diabetes if on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of these conditions. Grade **E**"
- "In people who are prescribed second-generation antipsychotic medications, screen for prediabetes and diabetes at baseline and repeat 12–16 weeks after medication initiation or sooner, if clinically indicated, and annually. Grade **B**"
- "People with HIV should be screened for diabetes and prediabetes with an FPG 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, FPG should be checked annually. Grade **E**"

Children & Adolescents (Ch 14)

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:

- "Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or ≥10 years of age, whichever occurs earlier, in youth with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes."46 Grading based on risk factors;
- 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.[46]
- "If tests are normal, repeat screening at a minimum of 3-year intervals [Grade E], or more frequently if BMI is increasing [Grade **C**]."
- "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**
- "Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes." 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)"
- "A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children" Grade **B**.[49]

Pregnancy (Ch 15)

- "...although A1c may be useful, it should be used as a secondary measure of glycemic control in pregnancy, after blood glucose monitoring."
- "Fasting, preprandial, and postprandial blood glucose monitoring are recommended in individuals with diabetes in pregnancy to achieve optimal glucose levels. Glucose goals 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) Grade **B**"
- "Due to increased red blood cell turnover, A1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C goal in pregnancy is <6% (<42 mmol/mol) if this can be achieved without significant hypoglycemia, but the goal 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 four to twelve 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 three-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, individuals with GDM should be tested for persistent diabetes or prediabetes at four to twelve weeks postpartum with a fasting 75-g OGTT using nonpregnancy criteria as outlined in Section two, "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."
- "Individuals with a history of GDM should have ongoing screening for prediabetes or type 2 diabetes every 1–3 years, even if the results of the initial 4–12 week postpartum 75-g OGTT are 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 thresholds for nonpregnant individuals)."[50]

Heart Failure Considerations (ch. 10)

- "In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated." Grade **A**
- "Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms; signs or symptoms of associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves)." Grade **E**
- "Adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NTproBNP]) to facilitate prevention of stage C heart failure." Grade **B**
- "In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure." Grade **A**
- "In asymptomatic individuals with diabetes and age ≥50 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes, screening for PAD with ankle-brachial index testing is recommended to guide treatment for cardiovascular disease prevention and limb preservation. A In individuals with diabetes duration ≥10 years, screening for PAD should be considered" Grade B.[51]

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis & Chronic Kidney Disease (ch. 4 and ch. 11)
From chapter 4:

- "Adults with type 2 diabetes or prediabetes, particularly those with obesity or cardiometabolic risk factors or established cardiovascular disease, should be screened/risk stratified for clinically significant liver fibrosis (defined as moderate fibrosis to cirrhosis) using a calculated fibrosis-4 index (FIB-4) (derived from age, ALT, AST, and platelets...even if they have normal liver enzymes." Grade **B**
- "Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for >6 months and low FIB-4 should be evaluated for other causes of liver disease." Grade **B**
- "Adults with type 2 diabetes or prediabetes with an indeterminate or high FIB-4 should have additional risk stratification by liver stiffness measurement with transient elastography or the blood biomarker enhanced liver fibrosis (ELF)." Grade **B**
- "Adults with type 2 diabetes or prediabetes with indeterminate results or at high risk for significant liver fibrosis (i.e., by FIB-4, liver stiffness measurement, or ELF) should be referred to a gastroenterologist or hepatologist for further workup. Interprofessional care is recommended for long-term management Grade **B**."[52,53]

From chapter 11:

Additionally: "A screening strategy based on elevated plasma aminotransferases >40 units/L would miss most individuals with NASH in these settings, as clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L. The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals, as higher levels are associated with increased liver-related mortality, even in the absence of identifiable risk factors. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count."[54]

In regards to A1c and NASH, the ADA restricts its comments to the following: "The only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C goal of 7%) and blood pressure control (blood pressure <130/80 mmHg)," and "Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large, randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes and type 2 diabetes. Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that lowering blood glucose itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C goals."[54]

Hospital Care Delivery Standards and Perioperative Care (ch. 16)

- "Perform an A1C test on all people with diabetes or hyperglycemia (random blood glucose >140 mg/dL [>7.8 mmol/L]) admitted to the hospital if no A1C test result is available from the prior 3 months." Grade **B**
- "In hospitalized individuals with diabetes who are eating, point-of-care (POC) blood glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h. More frequent POC blood glucose monitoring ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin therapy." (No grade; statement)

The following approach may be considered for those in preoperative and perioperative care:

- "A preoperative risk assessment should be performed for people with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
- The A1C goal for elective surgeries should be <8% (<63.9 mmol/L) whenever possible.
- The blood glucose goal in the perioperative period should be 100–180 mg/dL (5.6–10.0 mmol/L) within 4 h of the surgery. CGM should not be used alone for glucose monitoring during surgery.
- Metformin should be held on the day of surgery.
- SGLT2 inhibitors should be discontinued 3–4 days before surgery.
- Hold other oral glucose-lowering agents the morning of surgery or procedure and give one-half of NPH dose or 75–80% doses of long-acting analog insulin or adjust insulin pump basal rates based on the type of diabetes and clinical judgment.
- Monitor blood glucose at least every 2–4 h while the individual takes nothing by mouth and dose with short- or rapid-acting insulin as needed.
- There is little data on the safe use and/or influence of GLP-1 receptor agonists on glycemia and delayed gastric emptying in the perioperative period.
- Stricter perioperative glycemic goals are not advised, as perioperative glycemic goals stricter than 80–180 mg/dL (4.4–10.0 mmol/L) may not improve outcomes and are associated with more hypoglycemia.
- Compared with usual dosing, a reduction by 25% of basal insulin given the evening before surgery is more likely to achieve perioperative blood glucose goals with a lower risk for hypoglycemia.
- In individuals undergoing noncardiac general surgery, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic outcomes and lower rates of perioperative complications compared with the reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing."[55]

The ADA did not specifically mention "bariatric surgery" in their hospital care delivery section (ch. 16).

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 three years in individuals ≥40 years of age or in individuals at high risk on a risk calculator (33% chance of developing diabetes over ten 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 three 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 six 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 three 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 six to twelve 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."[56]

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 three years may be a reasonable approach for adults with normal blood glucose levels."[57]

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.[58] An "I" grade is defined by the USPSTF as "I Statement- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined."[59]

In 2022, the USPSTF released its first recommendation on screening for type 2 diabetes in children and adolescents. This recommendation applies to children and adolescents who are not pregnant and who are younger than 18 years of age without known diabetes or prediabetes and who are without symptoms of diabetes or prediabetes. The USPSTF states that the goal of screening for type 2 diabetes in young people is "to diagnose and treat it early to prevent development of bad health outcomes. However, no studies have looked at the link between screening for type 2 diabetes in children and adolescents and bad health outcomes. Studies about the effect of type 2 diabetes treatment on health outcomes in children and adolescents have not had enough patients with bad outcomes to draw any meaningful conclusions. No studies have looked at harms of screening for type 2 diabetes in young people. Potential harms may include side effects from medications used to treat diabetes, such as low blood glucose, nausea, or vomiting." Based on the current evidence for asymptomatic children and adolescents younger than 18 years of age, the USPSTF concluded that "current evidence is insufficient to assess the balance of benefits and harms of screening for type 2 diabetes in children and adolescents" and has given it an "I" grade.[60]

World Health Organization (WHO)

The Global Report on Diabetes 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."[61]

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 three months" if the patient is stabilized as a result of the insulin treatment.[62]

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 thirty-five to seventy 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 three years to be a reasonable approach.[63]

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 two years for patients 65 years or older. FPG 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.[64]

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:

- Three to six months (tailored to individual needs) until HbA1c is stable on unchanging therapy.
- Six 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) standardization."

"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."[65]

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:
  - Asian
  - African American
  - Hispanic
  - Native American (Alaska Natives and American Indians)
  - 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 5 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 three years for individuals with normal results. Consider annual screening for patients with two 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."[66] 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 ≥ eight hours of an overnight fast), or
- Plasma glucose (PG) concentration ≥200 mg/dL two hours after ingesting a 75-g oral glucose load after an overnight fast of at least eight hours, or
- Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (nonfasting) PG concentration ≥200 mg/dL, or
- A1C level ≥6.5%

Diagnosis of DM requires two abnormal test results, either from the same sample or two 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 IFG (100 to 125 mg/dL), impaired glucose tolerance (IGT), which is a PG value of 140 to 199 mg/dL two 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 individuals 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 individuals for GDM at twenty-four to twenty-eight weeks' gestation. Diagnose GDM with either the one-step or the two-step approach.

- The one-step approach uses a two-hour 75-g oral glucose tolerance test (OGTT) after ≥ eight hours of fasting with diagnostic cutoffs of one or more FPG ≥92 mg/dL, one-hour PG ≥180 mg/dL, or two-hour PG ≥153 mg/dL.
- The two-step approach uses a nonfasting one-hour 50-g glucose challenge test with one-hour PG screening threshold of 130 or 140 mg/dL. For individuals with a positive screening test, the three-hour 100-g OGTT is used for diagnosis with two 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 six months of age have a monogenic cause as autoimmune T1D rarely occurs before six 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 includes the following:

- "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 two 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 individuals should be screened for GDM at twenty-four to twenty-eight weeks’ gestation. Universal screening is recommended, as selective screening (only in individuals with risk factors) would miss a significant number of individuals with GDM and universal screening has been shown to be cost-effective compared with selective screening.”[66]

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 three 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.”[67]

In 2023, the AACE/ACE released “Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus.”[68]

Diagnosis related recommendations:

- “Fasting glucose should be measured in venous plasma when used to establish the diagnosis of diabetes, with a value ≥7.0 mmol/L (≥126 mg/dL) diagnostic of diabetes. A (high)”

Screening related recommendations:

- “Recommendation: Screening by HbA1c, FPG, or 2-h OGTT is recommended for individuals who are at high risk of diabetes. If HbA1c is <5.7% (<39 mmol/mol), FPG is <5.6 mmol/L (<100 mg/dL), and/or 2-h plasma glucose is <7.8 mmol/L (<140 mg/dL), testing should be repeated at 3-year intervals. B (moderate)
- Recommendation: Glucose should be measured in venous plasma when used for screening of high-risk individuals. B (moderate)
- Recommendation: Plasma glucose should be measured in an accredited laboratory when used for diagnosis of or screening for diabetes. GPP (good practice point)”

Monitoring/Prognosis:

- “Recommendation: Routine measurement of plasma glucose concentrations in a laboratory is not recommended as the primary means of monitoring or evaluating therapy in individuals with diabetes. B (moderate)”

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 four 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.”[69]

American College of Gastroenterology

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition where there is a buildup of fat in the liver. It is seen in individuals who drink little to no alcohol but who have diabetes, obesity, high blood pressure, or high cholesterol. Diabetes is both a possible cause of and or symptom of MASLD: while diabetes is a risk factor for developing MASLD, individuals who have been diagnosed with MASLD may be at risk for developing heart disease and diabetes.[70]

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Coding Section

Codes	Number	Description
CPT	82947	Glucose; quantitative, blood (except reagent strip)
	82951	Glucose; tolerance test (GTT), 3 specimens (includes glucose)
	82952	Glucose; tolerance test, each additional beyond 3 specimens
	82985	Glycated protein
	83036	Hemoglobin; glycosylated (A1C)
	83037	Hemoglobin; glycosylated (A1C) by device cleared by FDA for home use
ICD-10-CM	E08.00 – E10.9	Type 1 diabetes
	E11.10 (effective 1/1/2018)	Type 2 diabetes mellitus with ketoacidosis without coma
	E11.00 – E13.8	Type 2 diabetes
	E13.00 – E13.9	Other specified diabetes mellitus without complications
	E28.2	Polycystic ovary syndrome
	E66.01 – E66.09	Obesity/overweight
	E78.5	Dyslipidemia, Hyperlipidemia, unspecified
	E88.81	Metabolic syndrome
	E88.89	Other specified metabolic disorders
	E88.9	Metabolic disorder, unspecified
	I00 – I51.9	Diseases of the circulatory system
	I21.9	Acute myocardial infarction, unspecified
	I21.A1	Myocardial infarction Type 2
	I21.A9	Other myocardial infarction type
	I50.810	Right heart failure, unspecified
	I50.811	Acute right heart failure
	I50.812	Chronic right heart failure
	I50.813	Acute on chronic right heart failure
	I50.814	Right heart failure due to left heart failure
	I50.82	Biventricular heart failure
	I50.83	High output heart failure
	I50.84	End stage heart failure

	I50.89	Other heart failure
	L83	Acanthosis nigricans
	O24.410 – O24.439	Gestational diabetes
	R73.01 – R73.09	Other abnormal glucose
	R7303	Prediabetes
	Z13.1	Screening for diabetes mellitus
	Z68.53	Body mass index (BMI) pediatric, 85th percentile to less than 95th percentile for age
	Z68.54	greater than or equal to 95th percentile for age
	Z72.3	Lack of physical exercise
	Z83.3	Family hx diabetes mellitus
	Z86.32	Personal history of gestational diabetes
	Z86.71 – Z86.79	Personal hx cardiovascular disease

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

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community and other nonaffiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

History From 2016 Forward

10/07/2025 Annual review, no change to policy intent. Updating description, table of terminology, rationale, and references.
01/16/2025 Annual review, adding new statement criteria #2e and #5i, removing note #1. Also updating description, table of term, rat, and ref.
12/10/2024 Added Code CPT 82947 to coding section. No other change made.
01/24/2024 Annual review, policy verbiage updated for clarity and consistency, criteria #11 is being added to address situations not covered in the first 10 criteria. Criteria #4 is being added to address asymptomatic adults 35 years of age and older. Also updating note #1, note #3, rationale and references.
05/02/2023 Annual review, updating the entire policy for clarity and consistency.
08/11/2022 Interim review, removing BMI statement in coverage criteria, adding note at the end of the coverage criteria. Also some updating for clarity of the policy verbiage. Updating description, rationale and references.
10/01/2021 Annual review, no change to policy intent. Updating background, rationale and references.
10/01/2020 Annual review, no change to policy intent, but, medical necessity criteria have been reworded for clarity and to meet ADA updated definitions. Also updating description, coding, rationale and references.
10/21/2019 Annual review, updating policy to allow testing for pregnant members as frequently as monthly. Also updating coding.
11/01/2018 Annual review, medical necessity criteria updated to be in line with 2018 ADA recommendations. Adding codes E78.5, E88.89, E88.81 and E88.9 to the coding section. No other changes made.
11/29/2017 Correcting technical error in coding section. No other changes
10/30/2017 Updating policy section and updating coding section. No other changes made.
10/23/2017 Annual review, no change to policy intent.
09/28/2017 Updated coding with 2018 coding. No other changes.
04/26/2017 Updated category to Laboratory. No other changes.
03/06/2017 Updated coding to add Z86.32.
11/07/2016 Interim review, adding atypical antipsychotics to the second bullet in the policy verbiage.
05/31/2016 Interim review to update policy criteria # 3
05/02/2016 Interim update to add CPT code 81506.
01/07/2016 NEW POLICY