2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2026

*American Diabetes Association Professional Practice Committee for Diabetes**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee for Diabetes, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia (1). Diabetes can be diagnosed by demonstrating increased concentrations of glucose in venous plasma or increased A1C in the blood. Diabetes is classified conventionally into several clinical categories (e.g., type 1 or type 2 diabetes, gestational diabetes mellitus, and other specific types derived from other causes, such as monogenic diabetes, exocrine pancreatic disorders, and high-risk medications) (2).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on A1C or plasma glucose criteria. Plasma glucose criteria include either the fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG) during a 75-g oral glucose tolerance test (OGTT), or random glucose accompanied by classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, and unexplained weight loss) or hyperglycemic crises (i.e., diabetic ketoacidosis [DKA] and/or hyperglycemic hyperosmolar state [HHS]) (**Table 2.1**).

Recommendations

2.1a Diagnose diabetes based on A1C or plasma glucose criteria. Plasma glucose criteria include either fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG) during a 75-g oral glucose tolerance test (OGTT), or random glucose accompanied by classic hyperglycemic symptoms or crises (**Table 2.1**). **B**

2.1b In the absence of unequivocal hyperglycemia (e.g., hyperglycemic crises), diagnosis requires confirmatory testing (**Table 2.1**). **B**

**A complete list of members of the American Diabetes Association Professional Practice Committee for Diabetes can be found at https://doi.org/10.2337/dc26-SINT.*

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Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests, which may be obtained at the same time (e.g., A1C and FPG), or the same test at two different time points.

Screening and Diagnosis of Diabetes

FPG, 2-h PG during 75-g OGTT, and A1C are appropriate for screening and diagnosis. It should be noted that detection rates of different screening tests vary in both populations and individuals. FPG, 2-h PG, and A1C reflect different aspects of glucose metabolism, and diagnostic cut points for the different tests will identify groups with incomplete concordance (3). Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (4). Moreover, the efficacy of interventions for primary prevention of type 2 diabetes (i.e., preventing conversion of prediabetes to type 2 diabetes) has been demonstrated mainly among individuals with prediabetes who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria (5–8).

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (9) (**Table 2.1** and **Table 2.2**). Diabetes may be identified anywhere along the spectrum of clinical scenarios—in seemingly low-risk individuals who coincidentally undergo glucose monitoring, in individuals screened based on diabetes risk assessment, and in individuals with symptoms and signs of hyperglycemia. There is presently insufficient evidence to support the use of continuous glucose monitoring (CGM) for screening or diagnosis of prediabetes or diabetes. For additional details on the evidence used to establish the criteria for the diagnosis of diabetes or prediabetes, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (2) and other reports (1,3,10,11).

Table 2.2—Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

Use of Fasting Plasma Glucose or 2-Hour Plasma Glucose for Screening and Diagnosis of Diabetes

In the clinical scenario where a person has classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, unexplained weight loss) or presents with hyperglycemic crisis, measurement of random plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]). In these cases, knowledge of the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. In this context, testing A1C helps determine the chronicity of hyperglycemia. However, in an individual without symptoms, FPG or 2-h PG can be used for screening and diagnosis of diabetes. In nonpregnant individuals, FPG (or A1C) is typically preferred for routine screening due to the ease of administration (**Table 2.3**); however, the 2-h PG (OGTT) testing protocol is significantly more sensitive than the other two tests and is preferentially recommended for screening for some conditions (e.g., cystic fibrosis–related diabetes or post-transplantation diabetes mellitus). In the absence of classic symptoms of hyperglycemia, repeat testing is required to confirm the diagnosis regardless of the test used (see CONFIRMING THE DIAGNOSIS, below).

Major advantages of glucose monitoring are its low cost and availability. Disadvantages include the high diurnal variation in glucose and the 8-h fasting requirements (**Table 2.3**). Recent physical activity, illness, or acute stress can affect glucose concentrations. Glycolysis is also an important and underrecognized concern with glucose testing. Glucose concentrations will be falsely low if samples are not processed and analyzed promptly (1).

People should follow a mixed eating pattern with at least 150 g of carbohydrates on the 3 days prior to OGTT (12–14). Antecedent carbohydrate restriction in the days prior to OGTT can falsely elevate postchallenge glucose levels, potentially resulting in a false-positive OGTT (12).

Use of A1C for Screening and Diagnosis of Diabetes

Recommendations

2.2a The A1C test should be performed using a method that is certified by the National Glycohemoglobin

Table 2.3—Considerations related to the use and interpretation of laboratory measurements of glucose and A1C

	Glucose	A1C
Cost	Inexpensive and available in most laboratories across the world	More expensive than glucose and not as widely available globally
Time frame of hyperglycemia	Acute measure	Chronic measure of glucose exposure over the past ~2–3 months
Preanalytic stability	Poor; plasma must be separated immediately or samples must be kept on ice to prevent glycolysis	Good
Sample	Measurement can vary depending on sample type (plasma, serum, whole blood) and source (capillary, venous, arterial)	Requires whole-blood sample
Assay standardization	Not standardized	Well standardized
Fasting	Fasting or timed samples required	Nonfasting test; no participant preparation is needed
Within-person variability	High	Low
Acute factors that can affect levels	Food intake, stress, recent illness, activity	Unaffected by recent food intake, stress, illness, activity
Other individual factors that can affect test results	Diurnal variation, medications, alcohol, smoking, bilirubin	Altered erythrocyte turnover (e.g., anemia, iron status, splenectomy, blood loss, transfusion, hemolysis, glucose-6-phosphate dehydrogenase deficiency, erythropoietin), HIV, cirrhosis, kidney failure, dialysis, pregnancy
Test interferences	Depends on specific assay: sample handling/processing time, hemolysis, severe hypertriglyceridemia, severe hyperbilirubinemia	Depends on specific assay: hemoglobin variants, severe hypertriglyceridemia, severe hyperbilirubinemia

Data are from Selvin (236).

Standardization Program (NGSP) as traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. **B**

2.2b Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to devices approved for diagnosis by the U.S. Food and Drug Administration at Clinical Laboratory Improvement Amendments–certified laboratories that perform testing of moderate complexity or higher by trained personnel. **B**

2.3 Evaluate for the possibility of a problem or interference with either test when there is consistent and substantial discordance between blood glucose values and A1C test results. **B**

2.4 In conditions associated with an altered relationship between A1C and glycemia, such as some hemoglobin variants, pregnancy, glucose-6-phosphate dehydrogenase deficiency, HIV, and conditions that may alter red blood cell turnover, plasma glucose criteria should be used to diagnose diabetes. **B**

The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) (ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Outside the U.S., some assays are NGSP certified but many more are International Federation of Clinical Chemistry (IFCC) certified (a similarly stringent process) (1).

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 management in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)–regulated and CLIA-waived settings. FDA-approved point-of-care A1C testing can be used in laboratories or sites that are CLIA certified and inspected and meet the CLIA quality standards. These standards include specified personnel requirements (including documented annual competency assessments) and participation three times per year in an approved proficiency testing program (1,15,16).

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting is not required), greater preanalytical stability, and fewer day-to-day perturbations during stress, changes in nutrition, or illness. However, it should be noted that there is lower sensitivity of A1C at the designated cut point compared with that of 2-h PG as well as limited access in some parts of the world (**Table 2.3**).

A1C reflects glucose bound to hemoglobin over the life span of the erythrocyte (~120 days) and is thus a "weighted" average that is more heavily affected by recent blood glucose exposure. Thus, clinically meaningful changes in A1C can be seen in <120 days. A1C is an indirect measure of glucose exposure, and factors that affect hemoglobin concentrations or erythrocyte turnover can affect A1C (e.g., thalassemia or folate deficiency) (**Table 2.3**). A1C may not be a suitable diagnostic test in people with anemia, people treated with erythropoietin, or people undergoing hemodialysis or HIV treatment (1,17). Some A1C assays can be affected by hemoglobin variants. For instance, an A1C assay without interference from

hemoglobin variants should be used in individuals with sickle cell trait. An updated list of A1C assays with interferences is available at ngsp.org/interf.asp. Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of Black individuals in the U.S., is associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with levels in individuals without the variant (18).

There is controversy regarding racial differences in A1C. Studies have found that Black individuals have slightly higher A1C levels (approximately 0.3%) than non-Hispanic White or Hispanic people (19–22). A more precise understanding of the genetic determinants of A1C in diverse populations (18) is the focus of ongoing investigations (23,24). While some genetic variants might be more common in certain race or ancestry groups, it is important that we do not use race or ancestry as proxies for poorly understood genetic differences. Reassuringly, studies have shown that the association of A1C with risk for complications appears to be similar in Black and non-Hispanic White populations (25).

Confirming the Diagnosis

In the absence of a clear clinical diagnosis (e.g., individual with classic symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]), confirmatory tests are necessary to establish the diagnosis. This can be accomplished by two abnormal screening test results, measured either at the same time (26) or at two different time points. If using samples at two different time points, it is recommended that the second test, which may be either a repeat of the initial test or a different test, be performed in a timely manner. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. Two different tests (such as A1C and FPG) both having results above the diagnostic threshold when collected at the same time or at two different time points would also confirm the diagnosis. On the other hand, if an individual has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of factors that may affect measured A1C or glucose levels. The diagnosis is made based on the confirmatory screening test. For example, if an individual meets the diagnostic criterion for A1C (two results ≥6.5% [≥48 mmol/mol]) but not FPG (<126 mg/dL [<7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Test results close to the diagnostic threshold should prompt the health care professional to educate the individual about the onset of possible symptoms of hyperglycemia and to repeat the test in 3–6 months.

Consistent and substantial discordance between glucose values and A1C test results should elicit additional follow-up to determine the underlying reason for the discrepancy (including evaluation for the possibility of an analytical problem or interference with either test) and its clinical implications, if any, for the individual (**Table 2.3**). In this context, alternative validated biomarkers of chronic hyperglycemia such as fructosamine and glycated albumin should be considered for monitoring glycemic management in people with diabetes.

CLASSIFICATION

Recommendation

2.5 Classify people with hyperglycemia into appropriate diagnostic categories to aid in personalized management. **E**

Diabetes is classified conventionally into several clinical categories, although these are being reconsidered based on genetic, metabolomic, and other characteristics and pathophysiology (1):

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adults)
2. Type 2 diabetes (due to a nonautoimmune progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes)

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining personalized therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes having onset only in adults and type 1 diabetes having onset only in children are not accurate, as both diseases occur in all age groups. Children with type 1 diabetes are often diagnosed in the setting of hallmark symptoms of polyuria/polydipsia, and approximately half present with DKA (27–29). The onset of type 1 diabetes may be more variable in adults, who may not present with the classic symptoms seen in children and may progress to insulin replacement more slowly (30,31). The features most useful in determination of type 1 diabetes include younger age at diagnosis (<35 years), lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and plasma glucose >360 mg/dL (>20 mmol/L) at presentation (32) (**Fig. 2.1**). Occasionally, people with type 2 diabetes may present with DKA (33) in the context of ketosis-prone diabetes, particularly members of certain racial, ethnic, and ancestral groups (e.g., Black and Hispanic/Latino adults) (27). The initial requirement for insulin replacement therapy in individuals presenting with ketosis-prone diabetes is generally transient. It is important for health care professionals to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis can occur in up to 40% of adults with new type 1 diabetes (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes). In comparison, individuals with maturity-onset diabetes of the young (MODY) may be misdiagnosed as having type 1 diabetes (32). Although difficulties in distinguishing diabetes type may occur in all age groups at onset, the diagnosis generally becomes more obvious in people with marked loss of β-cell function as they rapidly require insulin therapy (**Fig. 2.1**). Although not prospectively validated, the **AABBCC** approach is a useful tool to help distinguish

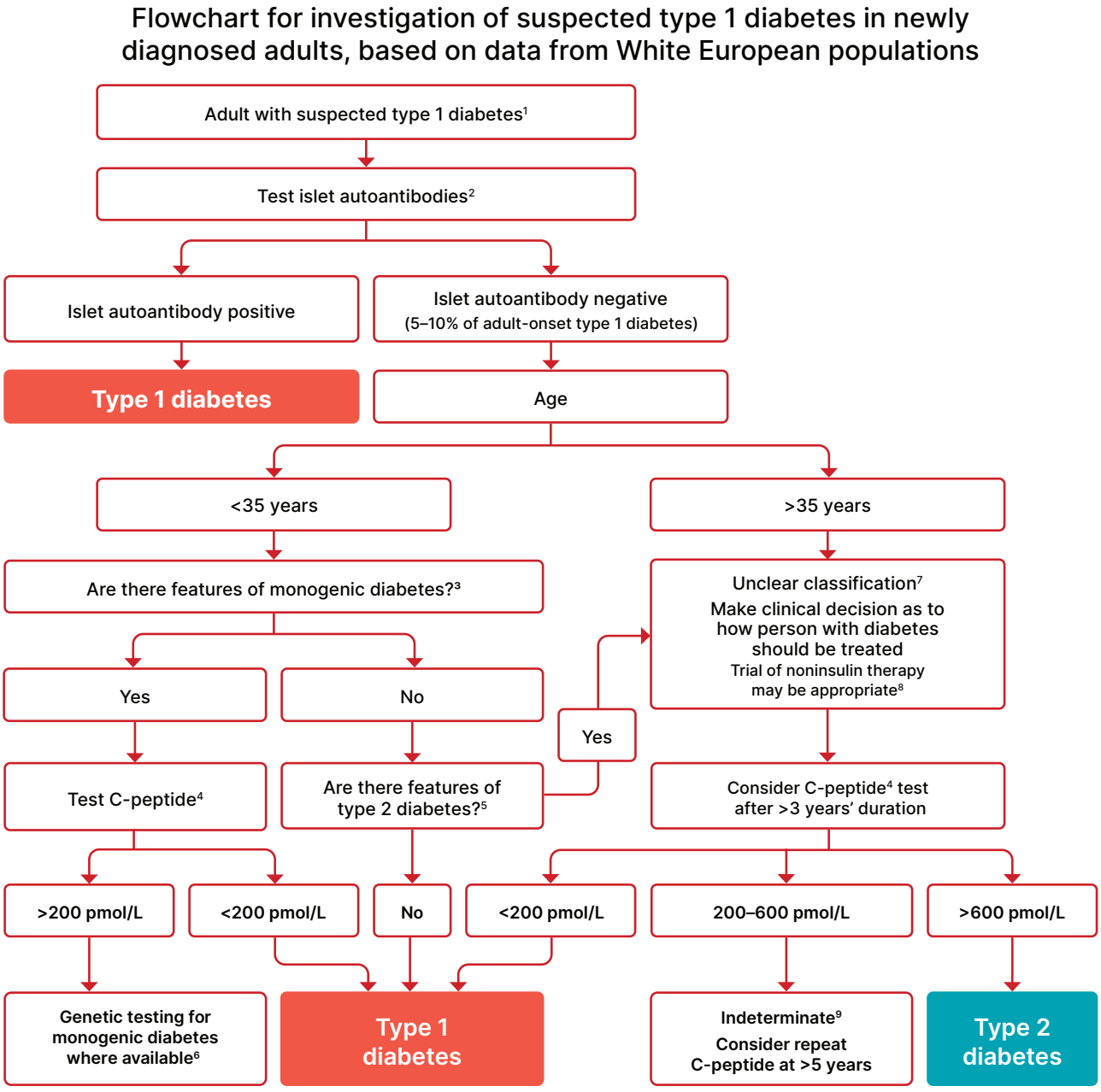

Figure 2.1—Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations. [1]No single clinical feature confirms type 1 diabetes in isolation. [2]Glutamic acid decarboxylase (GAD) should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA-2) and/or zinc transporter 8 (ZnT8) where these tests are available. In individuals who have not been treated with insulin, antibodies against insulin may also be useful. In those diagnosed at <35 years of age who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes, since 5–10% of people with type 1 diabetes do not have antibodies. [3]Monogenic diabetes is suggested by the presence of one or more of the following features: A1C <58 mmol/mol (<7.5%) at diagnosis, one parent with diabetes, features of a specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, and severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model probability >5% (diabetesgenes.org/exeter-diabetes-app/ModyCalculator). [4]A C-peptide test is only indicated in people receiving insulin treatment. A random sample (with concurrent glucose) within 5 h of eating can replace a formal C-peptide stimulation test in the context of classification. If the result is ≥600 pmol/L (≥1.8 ng/mL), the circumstances of testing do not matter. If the result is <600 pmol/L (<1.8 ng/mL) and the concurrent glucose is <4 mmol/L (<70 mg/dL) or the person may have been fasting, consider repeating the test. Results showing very low levels (e.g., <80 pmol/L [<0.24 ng/mL]) do not need to be repeated. Where a person is insulin treated, C-peptide must be measured prior to insulin discontinuation to exclude severe insulin deficiency. Do not test C-peptide within 2 weeks of a hyperglycemic emergency. [5]Features of type 2 diabetes include increased BMI (≥25 kg/m^2), absence of weight loss, absence of ketoacidosis, and less marked hyperglycemia. Less discriminatory features include non-White ethnicity, family history, longer duration and milder severity of symptoms prior to presentation, features of metabolic syndrome, and absence of a family history of autoimmunity. [6]If genetic testing does not confirm monogenic diabetes, the classification is unclear and a clinical decision should be made about treatment. [7]Type 2 diabetes should be strongly considered in older individuals. In some cases, investigation for pancreatic or other types of diabetes may be appropriate. [8]A person with possible type 1 diabetes who is not treated with insulin will require careful monitoring and education so that insulin can be rapidly initiated in the event of glycemic deterioration. [9]C-peptide values 200–600 pmol/L (0.6–1.8 ng/mL) are usually consistent with type 1 diabetes or maturity-onset diabetes of the young but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low BMI or after long duration. Reprinted and adapted from Holt et al. (32).

type 1 from type 2 diabetes: **A**ge (e.g., for individuals <35 years old, consider type 1 diabetes); **A**utoimmunity (e.g., personal or family history of autoimmune disease or polyglandular autoimmune syndromes); **B**ody habitus (e.g., BMI <25 kg/m^2); **B**ackground (e.g., family history of type 1 diabetes); **C**ontrol (preferred term is "goal," i.e., the inability to achieve glycemic goals on noninsulin therapies); and **C**omorbidities (e.g., treatment with immune checkpoint inhibitors for cancer can cause acute autoimmune diabetes) (34).

In both type 1 and type 2 diabetes, genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β-cell demise or dysfunction (35). Ongoing research efforts aim to combine clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are clustered into the current nomenclature with the goal of devising personalized treatment approaches (24). A diagnosis of type 1 diabetes does not preclude also having features classically associated with type 2 diabetes (e.g., insulin resistance, obesity, and other metabolic abnormalities), and until more precise subsets are used in clinical practice, it may be appropriate to categorize such an individual as having features of both type 1 and type 2 diabetes to facilitate access to glucose monitoring systems and appropriate treatment (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] or sodium–glucose cotransporter 2 [SGLT2] inhibitor therapies for potential weight and other cardiometabolic benefits).

Regarding the pathophysiology of type 1 diabetes, prospective studies showed that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes (36). In at-risk cohorts followed from birth or a very young age, seroconversion rarely occurs before 6 months of age and there is a peak in seroconversion between 9 and 24 months of age (37–39). The rate of progression from preclinical to symptomatic stages of type 1 diabetes is dependent on the age at first detection of an autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels may rise well before the clinical onset of diabetes (e.g., changes in FPG and 2-h PG can occur about 6 months before diagnosis) (40), making diagnosis feasible under ideal situations of serial monitoring of individuals at high risk of type 1 diabetes before the onset of DKA. The current paradigm of the progression of type 1 diabetes across three distinct stages (**Table 2.4**) also serves as a framework for research and regulatory decision-making (35,41).

There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. For this classification, all forms of diabetes mediated by autoimmune β-cell destruction independent of age of onset are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness that slow autoimmune β-cell destruction can occur in adults (42), thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA (31,43). There is evidence that relying on nonvalidated autoantibody tests for the diagnosis of LADA may lead to misclassification of some individuals with type 2 diabetes. Diagnostic accuracy of LADA may be improved by using higher-specificity tests and confirmatory testing for other autoantibodies and by restricting testing to those with clinical features suggestive of autoimmune diabetes (44).

The paths to β-cell demise and dysfunction are more heterogeneous in type 2 diabetes, but deficient β-cell insulin secretion and β-cell dysfunction, frequently in the setting of insulin resistance, appear to be common denominators. Type 2 diabetes is associated with insulin secretory defects related to genetic predisposition, epigenetic changes, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (24,35,45).

Table 2.4—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG, normal A1C	• Islet autoantibodies (usually multiple) • Dysglycemia: ○ IFG: FPG 100–125 mg/dL (5.6–6.9 mmol/L) or ○ IGT: 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) or ○ A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

Adapted from Skyler et al. (35). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (82). Dysglycemia can be defined by one or more criteria as outlined in the table.

TYPE 1 DIABETES

Recommendations

2.6 Screen for presymptomatic type 1 diabetes by testing autoantibodies against insulin (IA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), or zinc transporter 8 (ZnT8). **B**

2.7 Autoantibody-based screening for presymptomatic type 1 diabetes should be offered to those with a family history of type 1 diabetes or otherwise known elevated genetic risk. **B**

2.8a Individuals with screening results positive for one or more islet autoantibodies should be evaluated for stage 3 (overt) type 1 diabetes (using A1C, urinalysis, and/or plasma glucose), which would require prompt clinical management and education. **B**

2.8b Individuals with multiple confirmed islet autoantibodies and without overt type 1 diabetes have a high risk for progression to stage 3 type 1 diabetes and should be referred to a specialized center for metabolic staging (**Table 2.4**), education, and consideration of prevention trials or approved treatments (e.g., teplizumab). **B**

2.9 Individuals with a single confirmed IA-2 autoantibody should be monitored similarly to individuals with multiple islet autoantibodies, as IA-2 autoantibody positivity is an independent risk factor for progression. **B** Individuals with a single confirmed islet autoantibody should undergo repeat antibody testing every 6 months to 3 years (depending on age) to assess for persistence or seroconversion. **E**

2.10 Standardized islet autoantibody tests are recommended for classification of diabetes in adults who have phenotypic risk factors that overlap with those for type 1 diabetes (e.g., younger age at diagnosis, unintentional weight loss, ketoacidosis, or short time to insulin treatment). **E**

Immune-Mediated Diabetes

Autoimmune type 1 diabetes accounts for 5–10% of diabetes and is caused by autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase (GAD) (e.g., GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8). Clinical studies are being conducted to test various methods of preventing or delaying type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies) (36–38,43,46,47). The disease has strong HLA associations, with linkage to the *DQB1* and *DRB1* haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing (e.g., DRB1*0301-DQB1*0201 [DR3-DQ2] and DRB1*0401-DQB1*0302 [DR4-DQ8]) or protective (e.g., DRB1*1501 and DQA1*0102-DQB1*0602).

Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoantibodies and normoglycemia (**Table 2.4**). At stage 1, the 5-year risk of developing symptomatic type 1 diabetes is ∼44% overall but varies considerably based on number, titer, and specificity of autoantibodies as well as age of seroconversion and genetic risk (41). Stage 2 includes individuals with islet autoantibodies (usually multiple) and dysglycemia not yet diagnostic of diabetes (dysglycemia can be defined by one or more criteria as outlined in **Table 2.4**). At time of progression to stage 2, the risk of developing stage 3 type 1 diabetes is ∼60% within 2 years and ∼75% within 5 years (48,49).

Early diagnostic testing (**Table 2.4**) for stage 3 type 1 diabetes should be performed promptly in any individual with one or more islet autoantibodies to avoid delays in treatment, which can occur with long wait times for specialty referrals. Identifying overt hyperglycemia early can help prevent DKA at stage 3 diagnosis and guide urgency of referral. In the Diabetes Prevention Trial-Type 1, semiannual OGTT in high-risk family members was associated with a relatively low risk of DKA (4%) at disease presentation compared with individuals who had not been enrolled in a monitoring program (50). A consensus report provides guidance on when to perform repeat antibody testing, how metabolic status should be monitored, and how often these factors should be monitored in individuals with positive autoantibodies (51). A single autoantibody result requires metabolic evaluation, as some individuals may lose detectable antibodies as they approach stage 3. Specifically, individuals who have a single IA-2 autoantibody should be monitored at the same frequency as multiple-autoantibody–positive individuals, as they have a comparable risk of progressing through type 1 diabetes stages (52). For single non-IA-2 antibody positivity, progression risk is more heterogenous and depends on age, antibody type, and other risk factors. Evidence from pediatric cohorts shows that among children with a persistent single islet autoantibody, the 10-year cumulative risk of progression to clinical type 1 diabetes is ∼14–15%, with much of the risk accruing in the first 2 years after seroconversion and the highest risk being associated with younger age and single IA-2 autoantibody positivity (36). In adults, progression risk is lower and decreases with age, and prospective data to define an optimal cadence are limited; therefore, intervals are extrapolated from pediatric patterns and clinical diabetes expertise. The practical implication of this information is that the four islet autoantibodies (GAD autoantibody, IA-2 autoantibody, insulin autoantibody, ZnT8 autoantibody), a random venous or capillary blood glucose, and an A1C test should be repeated at intervals of 6 months to 3 years based on age. In children ≤3 years, test every 6 months for 3 years and then annually for 3 more years. In children and adolescents 3–18 years old, test annually and consider discontinuing after 3 years if no progression to multiple antibodies or onset of dysglycemia. In adults, test every 3 years or annually if additional risk factors are present, such as another autoimmune disease, elevated genetic risk score, or first-degree relative with type 1 diabetes (51).

In adults with stage 3 type 1 diabetes, isolated GAD autoantibody positivity is common and has been associated with slower loss of endogenous insulin production after diagnosis (32). In early stages of type 1 diabetes, single GAD65 autoantibody positivity is also associated with slower progression to stage 3 compared with IA-2 or ZnT8A autoantibody positivity (1,53).

The rate of β-cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults) (40,54). Children and adolescents often present with DKA as the first manifestation of the disease, and rates in the U.S. have increased over the past 20 years (27–29). Others have modest fasting hyperglycemia

that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission characterized by decreased insulin needs for months or years, but they eventually become insulin dependent and are at risk for DKA (30,31,55–57). At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Autoimmune destruction of β-cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals do not classically have obesity when they present with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders, such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"). Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (*FOXP3*) gene, and another disorder caused by the autoimmune regulator (*AIRE*) gene mutation (58,59).

Certain viruses have been associated with type 1 diabetes, including enteroviruses (e.g., Coxsackievirus B). During the early coronavirus disease 2019 (COVID-19) pandemic, several reports noted an increased incidence of hyperglycemia, DKA, and new-onset type 1 diabetes, raising the possibility that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a trigger or accelerator of disease in susceptible individuals (60). More recent large cohort and registry studies from multiple countries report mixed findings, with some showing a modest increased risk of type 1 diabetes following COVID-19 infection and others reporting that the association is largely due to challenges with health care access and diagnostic delays (61,62). These data suggest that both viral effects and indirect pandemic-related factors may have contributed to the initial observed spike of type 1 diabetes. Research is ongoing to clarify the long-term relationship between SARS-CoV-2 infection and type 1 diabetes risk, including the development of a global registry, the CoviDIAB Registry (63).

Immune Checkpoint Inhibitor–Induced Autoimmune Diabetes

The introduction of immunotherapy, specifically immune checkpoint inhibitors (ICIs), for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of autoimmune diabetes can occur with DKA and low or undetectable levels of C-peptide as a marker of endogenous β-cell function (64,65). Fewer than half of these individuals have islet autoantibodies, and most do not experience a phase of partial remission, which is commonly seen in type 1 diabetes, supporting the emerging view of a partially distinct pathophysiology. ICI-induced diabetes occurs in 0.6–1.4% of treated individuals and is more frequent with agents that block the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PDL-1) pathway, alone or in combination with other checkpoint inhibitors (e.g., anticytotoxic T-cell 4-antigen [CTLA-4] antibody) (66). Also, the majority of ICI-related cases of autoimmune diabetes occur in people with high-risk HLA susceptibility haplotype for type 1 diabetes; however, people with either a neutral or typically protective HLA haplotype for type 1 diabetes can also develop ICI-associated diabetes (67). To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications or caring for people who have a history of current or past exposure to these agents should be mindful of this adverse effect and educate and monitor individuals appropriately.

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. Individuals have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of people with type 1 diabetes fall into this category.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes are increasing (68). People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 25–50% are diagnosed with life-threatening DKA (27–29). Family history of type 1 diabetes increases the risk of developing type 1 diabetes compared with the general population, but the majority, ∼90%, of individuals who develop type 1 diabetes do not have a known relative with the disease. Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes (41), in children from the general population (69,70), or in children from the general population with high genetic risk (71) can identify many individuals who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (36). These findings are highly significant, because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (46,72,73). In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21% of 363 subjects with at least one autoantibody at 3 years of age (74). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and to prevent DKA (75,76). In several cohort studies, up to 50% of children with only a single autoantibody revert to being islet autoantibody negative during follow-up (77,78). Therefore, it is recommended that the first autoantibody-positive test be confirmed with a second test within 3 months, preferably in a laboratory that meets the performance standards set by the Islet Autoantibody Standardization Program (IASP) (51).

Type 1 diabetes genetic risk scores have been used in newborn screening to identify those at risk for future presentation of the disease. In a simulation

using one such genetic risk score, the majority of those who would go on to develop type 1 diabetes, >77%, could be identified within just 10% of the general population, identifying a subset who may most benefit from autoantibody testing (79). As many genetic risk studies have been performed in populations of European ancestry and discriminatory ability may differ in those of different ancestry, more large case-control cohorts from non-European populations are still needed (80).

Screening programs are available in Europe (e.g., Fr1da and gppad.org), Australia (e.g., type1screen.org), and the U.S. (e.g., trialnet.org, askhealth.org, and cascadekids.org). General population-based screening programs may offer broader testing where high-quality, validated assays and resources for appropriate follow-up of results are available, with several countries considering making such testing part of standard care. In 2023, Italy introduced nationwide screening for type 1 diabetes and celiac disease in the general population aged 1–17 years (81). Individuals who test autoantibody positive should be provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, and DKA prevention and should be given consideration for referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes (82).

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.11 Screening for risk of prediabetes and type 2 diabetes with an assessment of risk factors or validated risk calculator should be done in asymptomatic adults. **B**

2.12a Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors (**Table 2.5**). **B**

2.12b For all other people, screening should begin at age 35 years. **B**

2.12c In people without prediabetes or diabetes after screening, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain). **C**

2.13 To screen for prediabetes and type 2 diabetes, FPG, 2-h PG during 75-g OGTT, and A1C are each appropriate (**Table 2.1** and **Table 2.2**). **B**

2.14 When using OGTT as a screening tool for prediabetes or diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. **C**

2.15 Risk-based screening for prediabetes 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 factors for diabetes. (See **Table 2.6** for evidence grading of risk factors.) **B**

2.16a Consider screening people for prediabetes or diabetes if they are on certain medications, such as statins, thiazide diuretics, and some HIV medications, as these agents are known to increase the risk of these conditions. **C**

2.16b 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 thereafter. **B**

2.17 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. **E**

2.18 Monitor postprandial or random glucose levels with recurrent or long-term use of glucocorticoids. **B**

Table 2.5—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in individuals of Asian ancestry) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race, ethnicity, and ancestry (e.g., African American, Latino, Native American, Asian American)
   - History of cardiovascular disease
   - Hypertension (≥130/80 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or triglyceride level >250 mg/dL (>2.8 mmol/L)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans, metabolic dysfunction-associated steatotic liver disease)
2. People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have testing at least every 1–3 years.
4. For all other people, testing should begin at age 35 years.
5. 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.
6. Individuals in other high-risk groups (e.g., people with HIV, exposure to high-risk medicines, evidence of periodontal disease, history of pancreatitis) should also be closely monitored.

GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Prediabetes

Prediabetes is the term used to identify glucose or A1C levels that do not meet the criteria for diabetes yet fall in an intermediate range between normoglycemia and diabetes (25,83). People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (**Table 2.2**). Prediabetes is a significant risk factor for progression to diabetes as well as cardiovascular disease and several other cardiometabolic outcomes. Criteria for screening

Table 2.6—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- High-risk race, ethnicity, and ancestry **A** (see **Table 2.5**)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, large- or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile is deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

for diabetes or prediabetes in asymptomatic adults are outlined in **Table 2.5**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt a comprehensive screening for cardiovascular risk factors.

Diagnosis of Prediabetes

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (76,82) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (10). It should be noted that the World Health Organization and several diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L). The ADA also initially endorsed this IFG lower limit in 1997 (10). However, in 2003 the ADA adopted the new range of 100–125 mg/dL (5.6–6.9 mmol/L) to better define IFG so that the population at risk for developing diabetes with IFG would be comparable to that with IGT (11).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous curvilinear association between A1C and risk of diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5% and 6.0% (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9 to 25%). Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher than that with A1C of 5.0% (31 mmol/mol) (84). In a community-based study of Black and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (85). Another analysis also indicates that A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the Diabetes Prevention Program (DPP) and its follow-up (7).

An A1C range of 5.7–6.4% (39–47 mmol/mol) identifies a group of individuals at high risk for diabetes and cardiovascular outcomes. These individuals should be informed of their increased risk for diabetes and cardiovascular disease and counseled about effective strategies to lower their risks (see section 3, "Prevention or Delay of Diabetes and Associated Comorbidities"). Similar to glucose measurements, the continuum of risk is continuous and curvilinear: as A1C rises, the diabetes risk rises disproportionately (84). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [>42 mmol/mol] and individuals with both IFG and IGT).

Table 2.5 outlines the criteria for screening for prediabetes. The ADA risk test is an additional option (i.e., an awareness tool for the layperson and the health care professional) to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (diabetes.org/diabetes-risk-test). For additional background regarding risk factors and screening for prediabetes, see screening and testing for prediabetes and type 2 diabetes in asymptomatic adults and screening and testing for prediabetes and type 2 diabetes in children and adolescents, below. For details regarding individuals with prediabetes most likely to benefit from a formal behavioral or lifestyle intervention, see section 3, "Prevention or Delay of Diabetes and Associated Comorbidities."

Type 2 Diabetes

Type 2 diabetes accounts for 90–95% of all diabetes cases and encompasses individuals who generally have relative (rather than absolute) insulin deficiency in association with insulin resistance (i.e., decreased biological responses to insulin).

The heterogeneity of type 2 diabetes is increasingly recognized and is the subject of intense investigation (86). Although most people with type 2 diabetes have overweight or obesity, which alone causes some degree of insulin resistance, individuals who do not meet BMI criteria for overweight or obesity may have an increased distribution of body fat in the abdominal region, including sites involved in metabolic dysfunction–associated steatotic liver disease (MASLD) and/or ectopic sites (e.g., skeletal muscle).

DKA seldom occurs spontaneously in type 2 diabetes (27) but can arise in individuals with relative insulinopenia in the context of precipitating factors such as the stress of another illness (e.g., COVID-19 infection or myocardial infarction), use of illicit drugs (e.g., cocaine), or with the use of certain medications including glucocorticoids and SGLT2 inhibitors (87,88). HHS is more typically associated with type 2 diabetes (existing or new diagnosis) and is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. People with diabetes can also have mixed clinical features of both DKA and HHS (27).

Type 2 diabetes frequently goes undiagnosed for many years, because hyperglycemia develops gradually and, at earlier stages, may not be accompanied by classic symptoms and signs of hyperglycemia, such as blurry vision, dehydration, or unintentional weight loss. People with undiagnosed diabetes are exposed to variable degrees of untreated hyperglycemia and are at increased risk of

developing macrovascular and microvascular complications (89).

People with type 2 diabetes initially may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion that is insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Intensive lifestyle interventions and/or metabolic surgery can lead to diabetes remission (90–93) (see section 8, "Obesity and Weight Management for the Prevention and Treatment of Diabetes").

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity (94,95). It occurs more frequently in individuals with prediabetes, prior gestational diabetes mellitus, or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial, ethnic, and ancestral subgroups (**Table 2.5**). Finally, treatment with certain medications (e.g., glucocorticoids) can represent a significant risk factor for developing type 2 diabetes. In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing to exclude the diagnosis of type 1 diabetes (32) (**Fig. 2.1**).

Screening and Testing for Prediabetes and Type 2 Diabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes risk through a targeted assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the ADA risk test (diabetes.org/diabetes-risk-test), is recommended to guide health care professionals on whether performing a diagnostic test (**Table 2.1**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis, and simple tests to detect preclinical disease are readily available (96). The duration of glycemic burden is a strong predictor of adverse outcomes. When considering strategies to prevent the progression to diabetes in people with prediabetes, it is important to individualize the risk-to-benefit ratio of formal interventions and assess person-centered goals. Risk models have often found higher benefit of intervention in those at highest risk (97) (see section 3, "Prevention or Delay of Diabetes and Associated Comorbidities") and reduced the risk of diabetes complications (98) (see section 10, "Cardiovascular Disease and Risk Management," section 11, "Chronic Kidney Disease and Risk Management," and section 12, "Retinopathy, Neuropathy, and Foot Care"). In the National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (99) resulted in lower rates of developing retinopathy and nephropathy (100).

Despite the numerous benefits of screening and early diagnosis for prediabetes or diabetes, unfortunately many people in the U.S. and globally either remain undiagnosed or are diagnosed when complications have already arisen.

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic individuals are described below.

Age

Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people (101). Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

Medications

Screening for prediabetes or diabetes should be performed in people treated with certain medications, such as glucocorticoids, statins (102), thiazide diuretics, some HIV medications (103), and second-generation antipsychotic medications (104), as these drug classes increase the risk of glucose abnormalities, often by promoting insulin resistance.

Alone or in combination with other drugs, glucocorticoids are frequently used for the treatment of a diverse set of conditions including, but not limited to, autoimmune disease (e.g., rheumatoid arthritis), as part of the immunosuppression plan after transplant, or in conjunction with systemic anticancer therapy. The prevalence of glucocorticoid-induced diabetes (hyperglycemia in the absence of preexisting diabetes) depends on the drug's half-life, dose, and frequency of administration as well as the duration of treatment. In addition, the presence of common risk factors for diabetes (e.g., obesity) or concomitant use of other offending drugs (e.g., tacrolimus) may also play a role (105). Screening protocols for glucocorticoid-induced diabetes (and worsening hyperglycemia, in people with preexisting diabetes) are not implemented consistently, despite an incidence of up to 18–32% in people treated with supraphysiologic doses ($\geq$5 mg of prednisolone or equivalent alternative synthetic glucocorticoid) (106). Thus, educating individuals treated with recurrent or long-term courses of glucocorticoids regarding symptoms of hyperglycemia is essential (107). Of note, it is recommended that screening be performed by checking postprandial plasma glucose (possibly 1–2 h after meals) or random glucose rather than in the fasting state, as glucocorticoid-induced hyperglycemia generally results from insulin resistance. In fact, relying on fasting glucose as a screening test can lead to underdiagnosis and delayed treatment (105,108) (see also section 9, "Pharmacologic Approaches to Glycemic Treatment").

The ideal frequency of glucose monitoring for screening is not established, as a direct comparison of different monitoring schedules and their diagnostic performance is not available. In the outpatient setting, a proposed pragmatic approach is to check glucose twice weekly and to intensify frequency to daily monitoring if glucose is $\geq$200 mg/dL (109). In the context of cancer treatment, other organizations advocate for daily capillary glucose monitoring and prompt institution of treatment for glucose $\geq$220 mg/dL on two occasions (108,110,111). People treated with second-generation antipsychotic medications require close monitoring because of an increased risk of type 2 diabetes associated with this class of medications, often clustering with dyslipidemia and weight gain. People treated with these agents should be screened for prediabetes or diabetes at baseline, rescreened 12–16 weeks after medication initiation, and annually thereafter (112). Repeat testing can occur sooner if clinically warranted.

People With HIV

People living with HIV are at higher risk for developing prediabetes and diabetes. In addition, some antiretroviral (ARV) therapies may further increase the risk

(113). Therefore, a screening protocol for prediabetes and type 2 diabetes is recommended (114). As the A1C test may underestimate glycemia in people with HIV, plasma glucose criteria are preferred to diagnose prediabetes and diabetes (17).

Diabetes risk is increased with certain protease inhibitors (PIs) and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). New-onset diabetes is estimated to occur in more than 5% of individuals infected with HIV on PIs, whereas more than 15% may have prediabetes (115). PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the offending ARV agents if safe and effective alternatives are available (116). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, glucose-lowering agents may still be necessary.

Testing Interval

The appropriate interval between screening tests is not known (117). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced, and individuals with false-negative tests will be retested before substantial time elapses and complications develop (117). In especially high-risk individuals such as those with previous values nearer to the diabetes diagnostic cut point or ongoing treatment with medications listed above, shorter intervals between screenings may be useful.

Community Screening

Ideally, screening should be carried out within a health care setting (including appropriately resourced pharmacies) because of the need for follow-up and treatment (118). Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (119).

Screening in Dental Practices

Because of the bidirectional relationship between periodontal disease and diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (120,121). For example, one study estimated that 30% of individuals ≥30 years of age seen in general dental practices (including both people with and without periodontal disease) had newly diagnosed dysglycemia (121). Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting. For additional background on oral health in relation to prediabetes and type 2 diabetes, see section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities."

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents

The epidemiologic studies that formed the basis for the recommendations to use A1C and plasma glucose criteria to diagnose prediabetes and diabetes included only adult populations (122). However, ADA clinical guidance concluded that A1C, FPG, or 2-h PG also could be used to test for prediabetes or type 2 diabetes in children and adolescents (123).

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in certain high-risk racial, ethnic, and ancestral subgroups (124). See **Table 2.6** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (123). See **Table 2.1** and **Table 2.2** for the criteria for the diagnosis of diabetes and prediabetes, respectively, that apply to children, adolescents, and adults. See section 14, "Children and Adolescents," for additional information on type 2 diabetes in children and adolescents.

DIABETES INDUCED BY SYSTEMIC ANTI-CANCER THERAPY

Recommendations

2.19 People starting cancer treatment with immune checkpoint inhibitors (ICIs), including anti-PD-1 or anti-PDL-1 therapy (e.g., nivolumab, pembrolizumab, avelumab), phosphoinositidylinositol 3-kinase α (PI3Kα) inhibitors (e.g., alpelisib, inavolisib), or mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus), should be educated regarding risks, symptoms, and signs of hyperglycemia and hyperglycemic crises. **E**

2.20 In people treated with ICIs, fasting or random plasma glucose should be tested before initiating treatment, during each visit, or if symptoms and signs of hyperglycemia develop during or after treatment cessation. **E**

2.21 In people treated with PI3Kα inhibitors, fasting or random plasma glucose and A1C should be tested before initiating treatment, and random plasma glucose should be tested weekly for the first 2 weeks of treatment and then every 4 weeks during treatment. **C** Consider testing A1C every 3 months during treatment. **E**

2.22 In people treated with mTOR inhibitors, fasting or random plasma glucose should be tested before starting and at each visit throughout the duration of treatment. Consider testing A1C every 3 months during treatment. **C**

Both acute and chronic endocrine disorders account for a large portion of adverse events reported with cancer treatment (125). Hyperglycemia occurs in 15–50% of people receiving systemic anticancer treatment, as a direct effect of chemotherapeutic agents (e.g., busulfan) or the frequently associated glucocorticoid treatment (126), and represents a risk factor for poor cancer- and treatment-related outcomes (127,128). In this context, people treated with chemotherapy, glucocorticoids, immunotherapy or inhibitors of the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway should be provided with education and counseling regarding symptoms of hyperglycemia and glucose testing tools. Specifically,

regarding ICIs, PD-1 (e.g., nivolumab) and PDL-1 inhibitors (e.g., durvalumab) and, to a lesser extent, anti-CTLA-4 antibodies (e.g., ipilimumab), are associated with new-onset autoimmune diabetes in addition to other immune-related adverse events. ICI-induced autoimmune diabetes occurs in 0.6–1.4% of treated people, often presents as DKA, and almost invariably requires lifelong insulin therapy (129). Despite a peak of incidence within 2–3 months from the initiation of treatment (67,130), new onset of ICI-induced diabetes can occur anytime during treatment and has been reported even after discontinuation of ICIs (65,130). Similar to people with newly diagnosed type 1 diabetes, people who develop ICI-induced diabetes should be promptly referred to an endocrinologist and receive appropriate diabetes self-management education. Thus, testing either fasting or random plasma glucose before initiating treatment and at each visit (or for intervening symptoms of hyperglycemia) is a reasonable approach to increase health care professionals' awareness of the metabolic risk of ICIs and reduce the risk of presentation with DKA. Further epidemiological insight and validation of HLA-based risk prediction scores may guide future targeted screening strategies.

Inhibitors targeting the α isoform of PI3K have been approved (e.g., alpelisib, inavolisib) for the treatment of advanced or metastatic breast cancer. Pivotal trials demonstrated that PI3Kα inhibitors, when added to standard of care treatment, provided survival benefits but were also associated with the emergence of grade 3 or 4 hyperglycemia in up to 36% of participants, which was the most common reason for drug discontinuation (131,132). A retrospective analysis of adverse events accrued in a phase 3 randomized controlled trial (RCT) showed that the median time to onset for alpelisib-induced hyperglycemia was 13 days, with a range extending to approximately 1 year (133). The current data inform the recommendation to check fasting and random plasma glucose before initiating treatment and to monitor random plasma glucose weekly for the first 2 weeks of therapy and then every 4 weeks or sooner if symptoms of hyperglycemia develop in the interim. Testing A1C every 3 months can also be considered, while recognizing that alone A1C may not capture the early peak of hyperglycemia noted with PI3Kα inhibitors. Inhibitors of mTOR (e.g., everolimus) are associated with hyperglycemia of variable severity but without a definitive peak of onset. In a large meta-analysis that included 3,900 participants treated with everolimus across nine RCTs, the incidence of all-grade hyperglycemia was as high as 27%, whereas grades 3 and 4 were reported in 2.5% of participants (134). In a single-center retrospective cohort study in people with cancer treated with everolimus, the estimated median time to onset of hyperglycemia was 5–6 months, but the incidence distribution extended from a few weeks to several years after the initiation of treatment (135). In the absence of a clear-cut temporal pattern for the onset of hyperglycemia, fasting or random plasma glucose should be checked before treatment initiation and at each visit during treatment with mTOR inhibitors, or sooner if symptoms of hyperglycemia develop in the interim, while monitoring A1C every 3 months can also be considered.

Finally, hyperglycemia is also a relatively frequent complication of Akt inhibitors (e.g., capivasertib) and antibody drug conjugates (e.g., enfortumab vedotin), which will not be reviewed.

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Recommendation

2.23 Screen people for diabetes within 3–6 months following an episode of acute pancreatitis and annually thereafter. Screening for diabetes is recommended annually for people with chronic pancreatitis. **E**

Pancreatic diabetes (also termed pancreatogenic diabetes or type 3c diabetes) includes both structural (e.g., destruction or removal of normal pancreatic tissue) and functional loss of insulin secretion in the context of exocrine pancreatic insufficiency and is commonly misdiagnosed as type 2 diabetes. The diverse set of etiologies includes pancreatitis (acute and chronic pancreatic inflammation and associated fibrosis leading to loss of functional exocrine and endocrine pancreatic function), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed later in this section), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders, and idiopathic forms (2); as such, pancreatic diabetes is the preferred umbrella term (136).

Acute (even a single bout) and chronic pancreatitis can lead to postpancreatitis diabetes mellitus (137). A distinguishing feature is concurrent pancreatic exocrine insufficiency (consider screening individuals with acute and chronic pancreatitis for exocrine pancreatic insufficiency by measuring fecal elastase), pathological pancreatic imaging (endoscopic ultrasound, MRI, and computed tomography), and absence of type 1 diabetes–associated autoimmunity (138–141). Risk for microvascular complications appears to be similar to that of other forms of diabetes.

For people with pancreatitis and diabetes, glucose-lowering therapies potentially associated with increased risk of pancreatitis (i.e., incretin-based therapies) should be avoided. Early initiation of insulin therapy should be considered. In the context of pancreatectomy, islet autotransplantation can be considered for selected individuals with medically refractory chronic pancreatitis in specialized centers to preserve, fully or partially, endogenous islet function and insulin secretion (142,143).

Cystic Fibrosis–Related Diabetes

Recommendations

2.24a Annual screening for cystic fibrosis–related diabetes (CFRD) should begin by age 10 years in all people with cystic fibrosis, preferably using OGTT. **B**

2.24b If an OGTT is not feasible, A1C can be used as an alternative method as part of a two-step screening strategy. Individuals with A1C values between 5.5% and 6.4% (37 and 47 mmol/mol, respectively) should undergo an OGTT within 3 months. **C** An A1C value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD. **B**

2.25 Beginning 5 years after the diagnosis of CFRD, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis is an autosomal recessive multisystem condition arising from

recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Cystic fibrosis–related diabetes (CFRD) is a common comorbidity in people living with cystic fibrosis that is distinct from type 1 or type 2 diabetes and is often accompanied by pancreatic exocrine insufficiency (144). CFRD occurs in about 20% of adolescents and 50% of adults (145) and is associated with worse nutritional status and increased morbidity and mortality (146). Although insufficient insulin secretion is the primary defect in CFRD, insulin resistance can also occur in the setting of intervening illnesses and treatment with glucocorticoids. Current guidelines recommend screening for CFRD in people living with cystic fibrosis starting at age 10 years. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with IGT, no benefit has been established with respect to weight, height, BMI, or lung function (145). Based on its elevated predictive value (147), OGTT is the recommended screening test for CFRD in all people living with cystic fibrosis, if feasible, and should be repeated annually. However, engagement in current CFRD screening guidelines is poor, with only 30–40% of adults with cystic fibrosis having annual OGTTs (148,149).

In this context, other professional organizations have advocated for the use of A1C as part of a two-step screening strategy as an alternative to OGTT and to maximize the diagnostic yield of OGTT (150). Specifically, a retrospective study investigating the diagnostic performance of OGTT vis-à-vis A1C in 256 community-dwelling people living with cystic fibrosis, age 10–18 years, showed that A1C of 5.5% and 5.8% provided a sensitivity of 91% and 95%, respectively, to detect CFRD by OGTT (151). A1C 5.5% also afforded a negative predictive value for CFRD of approximately 98%, thus making A1C an effective first-line screening tool to identify people living with cystic fibrosis who should not undergo further testing with OGTT. In this framework alternative to the annual OGTT, only people living with cystic fibrosis with A1C 5.5–6.4% would proceed with OGTT. A1C ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD (152–154) and should be followed by a confirmatory test (preferably a repeat A1C or an OGTT, as the sensitivity of FPG is lower in people living with cystic fibrosis). Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (152,153). In the Cystic Fibrosis Foundation Patient Registry (155) that evaluated 3,553 people living with cystic fibrosis, of whom 13% had CFRD, early diagnosis and treatment of CFRD was associated with preservation of lung function. While CGM (156) may be more sensitive than OGTT for capturing early phases of dysglycemia, the lack of validated CGM thresholds or metrics to diagnose CFRD precludes, for now, recommending the use of CGM as a screening tool outside the research setting (145). There is inadequate evidence presently to alter CFRD screening based on use of highly effective CFTR modulator therapy, which uses small-molecule compounds that directly correct the basic defect of the CFTR channel and restore channel function (145).

Limited clinical trial data exist to inform optimal therapy for CFRD. People with CFRD should be treated with insulin to attain individualized glycemic goals. See section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information.

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.26 After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation diabetes mellitus (PTDM) is best made once the individual is stable on an immunosuppressive plan and in the absence of an acute infection. **B**

2.27 The OGTT is the preferred test to make a diagnosis of PTDM. **B**

2.28 Immunosuppressive plans shown to provide the best outcomes for individuals and graft survival should be used, irrespective of PTDM risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (157). New-onset diabetes after transplantation (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes who were undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (158). Another term, posttransplantation diabetes mellitus (PTDM) (158,159), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset. The clinical importance of PTDM lies in its impact as a significant risk factor for cardiovascular disease and chronic kidney disease in solid-organ transplantation (157).

Hyperglycemia is very common during the early posttransplant period, with ∼90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (158–161). In most cases, such stress- or glucocorticoid-induced hyperglycemia resolves by the time of discharge (161,162). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression (158). Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, and obesity) and transplant-specific factors, such as use of immunosuppressant agents (163–165). Whereas hyperglycemia in the early period after transplantation is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the individual is stable on maintenance immunosuppression (usually 3 months) and in the absence of acute infection (158,161–163,166).

OGTT is the recommended test for the diagnosis of PTDM as early as 3 months posttransplant (158). However, screening people with FPG and/or A1C can identify high-risk individuals who require further assessment and may reduce the number of overall OGTTs required.

Few RCTs have reported on the short- and long-term use of glucose-lowering medications in the setting of PTDM (163,167,168). Most studies have reported that transplant individuals with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (161,163,169). Insulin therapy is the agent of choice for the management of hyperglycemia and diabetes in the hospital setting and can be continued

postdischarge. Noninsulin glucose-lowering therapies can also be used for long-term management. The choice of agent is usually made based on the side effect profile of the medication, possible interactions with the individual's immunosuppression plan, and potential cardiovascular and kidney benefits in individuals with PTDM (163). See section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information.

MONOGENIC DIABETES SYNDROMES

Recommendations

2.29a Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have genetic testing for neonatal diabetes. **A**

2.29b Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and have a family history of diabetes in successive generations (suggestive of an autosomal-dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY). **A**

2.29c In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β-cell dysfunction (e.g., neonatal diabetes and MODY) or insulin resistance syndromes (e.g., monogenic lipodystrophies) are present in a small fraction of people with diabetes (<5%) (170). **Table 2.7** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (171) and ISPAD 2022 clinical practice consensus guidelines (170).

Diagnosis of Monogenic Diabetes

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (170,172)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, and lacking other metabolic features, especially strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.6–8.5 mmol/L]), stable A1C between 5.6 and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed neonatal diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (32,172–175). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β-cell K_{atp} channel.

The ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing (32). Correct diagnosis has critical implications, because 30–50% of people with K_{ATP}-related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, with insulin therapy being the preferred treatment strategy.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 14 genes on different chromosomes identified to date (170). The most common forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

Correct diagnosis of monogenic forms of diabetes is critical because people who have them may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment plans and delays in diagnosing other family members (170). A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes (173–180) (**Fig. 2.1**). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in people with monogenic diabetes has been reported. Individuals in whom monogenic diabetes is suspected should have genetic testing. Genetic screening (i.e., next-generation sequencing) is increasingly available and cost-effective (170). Consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis and to address comprehensive cardiovascular risk.

A diagnosis of one of the three most common forms of MODY, HNF1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective personalized therapy (i.e., no therapy for GCK-MODY and sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). See section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information. Additionally, diagnosis can lead to identification of other affected family members and can indicate potential extrapancreatic complications in affected individuals.

GESTATIONAL DIABETES MELLITUS

Recommendations

2.30 In individuals who are planning pregnancy, screen those with risk factors (**Table 2.5**) **B** and consider testing all individuals of childbearing potential for undiagnosed prediabetes or diabetes. **E**

Table 2.7—Most common causes of monogenic diabetes

	Gene	Inheritance	Clinical features
MODY	*HNF1A*	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [>5 mmol/L]); low hs-CRP; sensitive to sulfonylureas
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically does not require treatment in nonpregnant individuals; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [<3 mmol/L])
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight (macrosomia) and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes			
Permanent	*KCNJ11*	AD	IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	ABCC8	AD	IUGR; rarely developmental delay; responsive to sulfonylureas
	INS	AD	IUGR; insulin requiring
	FOXP3	X-linked	Immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring
Transient	6q24 (*PLAGL1*, *HYMA1*)	AD for paternal duplications	IUGR; macroglossia; umbilical hernia; may be treatable with medications other than insulin

Adapted from Carmody et al. (171). AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

2.31a Before 15 weeks of gestation, test individuals with risk factors (**Table 2.5**) **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.

2.31b Before 15 weeks of gestation, screen for abnormal glucose metabolism (defined as A1C 5.9–6.4% [41–47 mmol/mol] or FPG 110–125 mg/dL [6.1–6.9 mmol/L]) to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes and are at high risk of a later gestational diabetes mellitus (GDM) diagnosis. **B**

2.32 Screen for GDM at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**

2.33 Screen individuals with GDM for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g OGTT and clinically appropriate nonpregnancy diagnostic criteria. **B**

2.34 Individuals with a history of GDM should have lifelong screening for the development of prediabetes or diabetes every 1–3 years. **B**

Definition

For many years, gestational diabetes mellitus (GDM) was defined as any degree of glucose intolerance that was first recognized during pregnancy (11) regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but it also has limitations. First, the best evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy (181–183). Ideally, undiagnosed diabetes should be identified preconception in individuals with risk factors or in high-risk populations (184–189), as they are likely to benefit from preconception care. The preconception care of people with known preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission (190). If individuals are not screened prior to pregnancy, universal early screening at <15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (**Table 2.5**), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify and address these health disparities (186–189). Diagnostic criteria

for identifying undiagnosed diabetes in early pregnancy are the same as those used in nonpregnant individuals (**Table 2.1**). Individuals found to have diabetes should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as a fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (41 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, and perinatal death) and are at high risk of a later GDM diagnosis (191–194). Some, but not all, studies showed that an A1C threshold of 5.7% (39 mmol/L) was associated with adverse perinatal outcomes (193,195–197). Professional society guidance regarding early-pregnancy diagnosis and treatment of hyperglycemia less than overt diabetes differs (see section 15, "Management of Diabetes in Pregnancy").

If early screening for undiagnosed diabetes was negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation, and individuals not previously screened should be screened for GDM at the same time point (see section 15, "Management of Diabetes in Pregnancy"). The GDM diagnostic criteria for the 75-g OGTT from the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) and the GDM screening and diagnostic criteria with the two-step approach were not derived from data in the first half of pregnancy and should not be used for early screening (198).

Both the FPG and A1C are low-cost tests. An advantage of the A1C test is its convenience, as it can be added to the prenatal laboratory tests and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of conditions such as increased or decreased red blood cell turnover (usually decreases and increases A1C, respectively), hemoglobinopathies, and iron deficiency anemia (increases A1C) (199,200).

GDM is often indicative of underlying β-cell dysfunction (201), which confers markedly increased risk for later development of glucose intolerance and diabetes in the mother after delivery (202–204). Individuals diagnosed with GDM should receive lifelong screening for prediabetes and type 2 diabetes to allow prompt implementation of effective diabetes prevention interventions (205,206) and early treatment of diabetes (207).

Table 2.8—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when an individual is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1:

Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively),* proceed to a 100-g OGTT.

Step 2:

The 100-g OGTT should be performed when the individual is fasting.

The diagnosis of GDM is made when at least two> † of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [208]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (223). †ACOG notes that one elevated value can be used for diagnosis (223).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (208), a large-scale multinational cohort study completed by more than 23,000 pregnant individuals, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

GDM diagnosis (**Table 2.8**) can be accomplished with either of two strategies:

1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
2. The older "two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive based on the work of Carpenter-Coustan's interpretation of the older O'Sullivan and Mahan criteria (209).

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading experts to debate optimal strategies for the diagnosis of GDM.

One-Step Strategy

The IADPSG examined data from the HAPO study and defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in individuals at 24–28 weeks of gestation, wherein the cut points were those at which odds for adverse outcomes reached 1.75 times the estimated odds. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5 to 6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis (210). Many regional studies have seen a roughly one- to threefold increase in GDM cases using the IADPSG criteria (211). A study of pregnancy OGTTs with glucose levels blinded to caregivers found that 11 years after their pregnancies, individuals who would have been diagnosed with GDM by the one-step approach, as

compared with those without GDM, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the group identified as having GDM by the one-step approach would benefit from the increased screening for diabetes and prediabetes after pregnancy (212). The ADA recommends the IADPSG diagnostic criteria to optimize gestational outcomes, because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

Expected benefits of using IADPSG criteria for offspring are inferred from intervention trials focusing on individuals with lower levels of hyperglycemia than thoseidentified using older GDM diagnostic criteria.Those trials found modest benefits, including reduced rates of large-for-gestational-age births and preeclampsia (213, 214). Of note, 80–90% of participants being treated for mild GDM in these two RCTs could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped the thresholds recommended by the IADPSG, and in one trial (214), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]).

No RCTs of treating versus not treating GDM diagnosed by different criteria have been published to date. However, a randomized trial of testing for GDM at 24–28 weeks of gestation by the one-step method using IADPSG criteria versus the two-step method by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications (215), though concerns were raised about sample size estimates and unanticipated suboptimal engagement with the screening and treatment protocol. For example, in the two-step group, 165 participants not counted as having GDM were treated for isolated elevated FPG >95 mg/dL (>5.3 mmol/L) (216).

The one-step method identifies long-term risks of maternal prediabetes and diabetes as well as offspring glucose intolerance and adiposity. Post hoc GDM in individuals diagnosed with this method in the HAPO cohort was associated with higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucose levels during the OGTT; and reduced insulin sensitivity and oral disposition index in their offspring at 10–14 years of age compared with offspring of mothers without GDM. Associations of mother's fasting, 1-h, and 2-h values on the 75-g OGTT were continuous with a comprehensive panel of offspring metabolic outcomes (217,218). HAPO Follow-up Study (HAPO FUS) data demonstrate that neonatal adiposity and fetal hyperinsulinemia (cord C-peptide), both higher across the continuum of maternal hyperglycemia, are mediators of childhood body fat (219).

Data are lacking on how the treatment of mother's hyperglycemia in pregnancy affects her offspring's risk for obesity, diabetes, and other metabolic disorders (220,221). Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of individuals with GDM diagnosed by the one-step strategy.

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (222). The panel recommended continuing a two-step approach to screening that used a 1-h 50-g glucose loading test (GLT) followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (223). A 2021 U.S. Preventive Services Task Force systematic review concluded that one-step versus two-step screening is associated with increased likelihood of GDM (11.5% vs. 4.9%) but without improved health outcomes (224). The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (225).

Importantly, the NIH panel noted the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of individuals with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and therefore is easier to accomplish for many individuals. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (226), and shoulder dystocia without increasing small-for-gestational-age births. ACOG currently supports the two-step approach but notes that one elevated value, as opposed to two, may be used for the diagnosis of GDM (223). If this approach is implemented, the incidence of GDM will likely increase markedly. ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT Carpenter-Coustan or National Diabetes Data Group (227,228). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan and Mahan (209), which used whole blood and nonenzymatic methods for glucose determination. A secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (229) demonstrated that treatment was similarly beneficial in people meeting only the lower thresholds per Carpenter-Coustan (227) and in those meeting only the higher thresholds per National Diabetes Data Group (228). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds, as shown in step 2 in **Table 2.8**.

Future Considerations

Data exist to support each strategy, as demonstrated by differing recommendations by expert groups. A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method (230). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

The IADPSG criteria (one-step strategy) have been adopted internationally as the preferred approach. Data that compare population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (215,231–233). Pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria (234,235). There remains strong consensus that establishing

a uniform approach to diagnosing GDM will benefit people with GDM, caregivers, and policymakers. Longer-term outcome studies are currently underway.

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