2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

The American Diabetes Association (ADA) "Standards of Medical 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, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), 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, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a 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 (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (1).

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 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 occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both age-groups. Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with diabetic ketoacidosis (DKA) (2). The onset of

type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for insulin (3–5). Occasionally, patients with type 2 diabetes may present with DKA (6), particularly ethnic and racial minorities (7). It is important for the provider to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis is common (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes; individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes, etc.). Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the diagnosis becomes more obvious over time in people with β-cell deficiency.

In both type 1 and type 2 diabetes, various 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, patients 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 require better characterization of the many paths to β-cell demise or dysfunction (8). Across the globe many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing treatment approaches. Many of these studies show great promise and may soon be incorporated into the diabetes classification system (9).

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is now clear from studies of first-degree relatives of patients with type 1 diabetes that the persistent presence of two or more islet autoantibodies is a near certain predictor of clinical hyperglycemia and diabetes. The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose

and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (**Table 2.1**) and serve as a framework for future research and regulatory decision-making (8,10). 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. The clinical priority is awareness that slow autoimmune β-cell destruction can occur in adults leading to a long duration of marginal insulin secretory capacity. For the purpose of this classification, all forms of diabetes mediated by autoimmune β-cell destruction 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 of a population of adults likely to develop overt autoimmune β-cell destruction (11), thus accelerating insulin initiation prior to deterioration of glucose control or development of DKA (4,12).

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is associated with insulin secretory defects related to inflammation and metabolic stress among other contributors, including genetic factors. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (8,9,13–15).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria (16) (**Table 2.2**).

Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes (17,18) has mainly been demonstrated among individuals 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.

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (**Table 2.2** and **Table 2.5**) (19). Diabetes may be identified anywhere along the spectrum of clinical scenarios—in seemingly low-risk individuals who happen to have glucose testing, in individuals tested based on diabetes risk assessment, and in symptomatic patients.

Fasting and 2-Hour Plasma Glucose

The FPG and 2-h PG may be used to diagnose diabetes (**Table 2.2**). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (20). In people in whom there is discordance between A1C values and glucose values, FPG and 2-h PG are more accurate (21).

A1C

Recommendations

2.1 To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the NGSP and standardized to the Diabetes Control and Complications Trial (DCCT) assay. **B**

2.2 Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. **B**

2.3 In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used

Table 2.1—Staging of type 1 diabetes (8,10)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

to diagnose diabetes. (See OTHER CONDITIONS ALTERING THE RELATIONSHIP OF A1C AND GLYCEMIA below for more information.) **B**

The A1C test should be performed using a method that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic control in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)-regulated and CLIA-waived settings, only those point-of-care A1C assays that are also cleared by the FDA for use in the diagnosis of diabetes should be used for this purpose, and only in the clinical settings for which they are cleared. As discussed in Section 6 "Glycemic Targets" (https://doi.org/10.2337/dc21-S006), point-of-care A1C assays may be more generally applied for assessment of glycemic control in the clinic.

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress, changes in diet, or illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. The A1C test, with a diagnostic threshold of ≥6.5% (48 mmol/mol), diagnoses only 30% of the diabetes cases identified collectively using A1C, FPG, or 2-h PG, according to National

Health and Nutrition Examination Survey (NHANES) data (22).

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, such as hemodialysis, pregnancy, HIV treatment (23,24), age, race/ethnicity, pregnancy status, genetic background, and anemia/hemoglobinopathies. (See OTHER CONDITIONS ALTERING THE RELATIONSHIP OF A1C AND GLYCEMIA below for more information.)

Age
The epidemiologic studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations (22). However, recent ADA clinical guidance concluded that A1C, FPG, or 2-h PG can be used to test for prediabetes or type 2 diabetes in children and adolescents (see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below for additional information) (25).

Race/Ethnicity/Hemoglobinopathies
Hemoglobin variants can interfere with the measurement of A1C, although most assays in use in the U.S. are unaffected by the most common variants. Marked discrepancies between measured A1C and plasma glucose levels should prompt consideration that the A1C assay may not be reliable for that individual. For patients with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used. An updated list of A1C assays with interferences is available at www.ngsp.org/interf.asp.

African Americans heterozygous for the common hemoglobin variant HbS may have, for any given level of mean glycemia, lower A1C by about 0.3% compared with those without the trait (26). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African Americans, was associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with those without the variant (27).

Table 2.2—Criteria for the diagnosis of diabetes

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 WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

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

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia (28–30). For example, African Americans may have higher A1C levels than non-Hispanic Whites with similar fasting and postglucose load glucose levels (31). Though conflicting data exists, African Americans may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (32,33). Similarly, A1C levels may be higher for a given mean glucose concentration when measured with continuous glucose monitoring (34). Despite these and other reported differences, the association of A1C with risk for complications appears to be similar in African Americans and non-Hispanic Whites (35,36).

Other Conditions Altering the Relationship of A1C and Glycemia

In conditions associated with increased red blood cell turnover, such as sickle cell disease, pregnancy (second and third trimesters), glucose-6-phosphate dehydrogenase deficiency (37,38), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes (39). A1C is less reliable than blood glucose measurement in other conditions such as the postpartum state (40–42), HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) (23), and iron-deficient anemia (43).

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL [11.1 mmol/L]), diagnosis requires two abnormal test results, either from the same sample (44) or in two separate test samples. If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. 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. If two different tests (such as A1C and FPG) are both above the diagnostic threshold when analyzed from the same sample

or in two different test samples, this also confirms the diagnosis. On the other hand, if a patient 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 the possibility of A1C assay interference. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the 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.

Each of the tests has preanalytic and analytic variability, so it is possible that a test yielding an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with the patient and repeat the test in 3–6 months.

Diagnosis

In a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥200 mg/dL [11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some providers may also want to know the A1C to determine the chronicity of the hyperglycemia. The criteria to diagnose diabetes are listed in **Table 2.2**.

TYPE 1 DIABETES

Recommendations

2.4 Screening for type 1 diabetes risk with a panel of islet autoantibodies is currently recommended in the setting of a research trial or can be offered as an option for first-degree family members of a proband with type 1 diabetes. **B**

2.5 Persistence of autoantibodies is a risk factor for clinical diabetes

and may serve as an indication for intervention in the setting of a clinical trial. **B**

Immune-Mediated Diabetes

This form, previously called "insulin-dependent diabetes" or "juvenile-onset diabetes," accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (GAD65), insulin, the tyrosine phosphatases IA-2 and IA-2β, and zinc transporter 8 (ZnT8). Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of islet autoimmunity (www.clinicaltrials.gov and www.trialnet.org/our-research/prevention-studies) (12,45–49). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the *DQA* and *DQB* genes. These HLA-DR/DQ alleles can be either predisposing or protective (**Table 2.1**). There are important genetic considerations, as most of the mutations that cause diabetes are dominantly inherited. The importance of genetic testing is in the genetic counseling that follows. Some mutations are associated with other conditions, which then may prompt additional screenings.

The rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults) (50). Children and adolescents may present with DKA as the first manifestation of the disease. 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 or decreased insulin needs for months or years and eventually become dependent on insulin for survival and are at risk for DKA (3–5,51,52). At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity is increasingly common in the general population, and there is evidence that it may also be a risk factor for type 1 diabetes. As such, obesity should not preclude the diagnosis. 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," https://doi.org/10.2337/dc21-S004).

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of patients with type 1 diabetes fall into this category. Individuals with autoantibody-negative type 1 diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (possibly ketosis-prone diabetes). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may be intermittent. Future research is needed to determine the cause of β-cell destruction in this rare clinical scenario.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes is increasing (53). Patients with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and approximately one-third are diagnosed with life-threatening DKA (2). Multiple studies indicate that measuring islet autoantibodies in individuals genetically at risk for type 1 diabetes (e.g., relatives of those with type 1 diabetes or individuals from the general population with type 1 diabetes–associated genetic factors) identifies individuals who may develop type 1 diabetes (10). Such testing, coupled with education about diabetes symptoms and close follow-up, may enable earlier identification of type 1 diabetes onset. 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 (45). 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 (48,54,55). 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 (56).

There is currently a lack of accepted and clinically validated screening programs outside of the research setting; thus, widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. However, one should consider referring relatives of those with type 1 diabetes for islet autoantibody testing for risk assessment in the setting of a clinical research study (see www.trialnet.org). Individuals who test positive should be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are being conducted to test various methods of preventing and treating stage 2 type 1 diabetes in those with evidence of autoimmunity with promising results (see www.clinicaltrials.gov and www.trialnet.org).

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.6 Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**

2.7 Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) and who have one or more additional risk factors for diabetes (**Table 2.3**). **B**

2.8 Testing for prediabetes and/or type 2 diabetes should be considered in women with overweight or obesity planning pregnancy and/or who have one or more additional risk factor for diabetes (**Table 2.3**). **C**

2.9 For all people, testing should begin at age 45 years. **B**

2.10 If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable, sooner with symptoms. **C**

2.11 To test for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are equally appropriate (**Table 2.2** and **Table 2.5**). **B**

2.12 In patients with prediabetes and type 2 diabetes, identify and treat other cardiovascular disease risk factors. **A**

2.13 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factor for diabetes. (See **Table 2.4** for evidence grading of risk factors.) **B**

2.14 Patients with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3−6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. **E**

Prediabetes

"Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal (35,36). Patients

Table 2.3—Criteria for testing 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 Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 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. HIV

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

with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (**Table 2.5**). Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD). Criteria for testing for diabetes or prediabetes in asymptomatic adults is outlined in **Table 2.3**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (57,58) and IGT as 2-h PG during 75-g OGTT levels from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (59). It should be noted that the World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent 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 compared with A1C of 5.0% (31 mmol/mol) (60). In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (61). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (62), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (63). Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 3 "Prevention or Delay of Type 2 Diabetes," https://doi.org/10.2337/dc21-S003). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (60). 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]).

Table 2.5 summarizes the categories of prediabetes and **Table 2.3** the criteria for prediabetes testing. The ADA diabetes risk test is an additional option for assessment to determine the appropriateness of testing for diabetes or prediabetes in asymptomatic adults (**Fig. 2.1**) (diabetes.org/socrisktest). For additional background regarding risk factors and screening for prediabetes, see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN ASYMPTOMATIC ADULTS and also SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below.

Type 2 Diabetes

Type 2 diabetes, previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance.

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (202)

Testing should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:
- 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**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **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 deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

Table 2.5—Criteria defining prediabetes*

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)

OR

A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *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.

At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, patients with type 2 diabetes have overweight or obesity. Excess weight itself causes some degree of insulin resistance. Patients who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

DKA seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection, myocardial infarction, or with the use of certain drugs (e.g., corticosteroids, atypical antipsychotics, and sodium–glucose cotransporter 2 inhibitors) (64,65). Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms caused by hyperglycemia. Nevertheless, even undiagnosed patients are at increased risk of developing macrovascular and microvascular complications.

Patients with type 2 diabetes 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. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, exercise, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive diet and exercise or surgical weight loss have led to diabetes remission (66–72) (see Section 8 "Obesity Management for the Treatment of Type 2 Diabetes," https://doi.org/10.2337/dc21-S008).

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior gestational diabetes mellitus (GDM), with hypertension or dyslipidemia, with polycystic ovary syndrome, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes is poorly understood and under intense investigation in this era of precision medicine (13). In adults without traditional risk factors for type 2 diabetes and/or younger age, consider islet autoantibody testing (e.g., GAD65 autoantibodies) to exclude the diagnosis of type 1 diabetes.

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

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the ADA risk test (**Fig. 2.1**) (online at diabetes.org/socrisktest), is recommended to guide providers on whether performing a diagnostic test (**Table 2.2**) 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 of type 2 diabetes. Simple tests to detect preclinical disease are readily available. The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes (see Section 3 "Prevention or Delay of Type 2 Diabetes," https://doi.org/10.2337/dc21-S003) and reduce the risk of diabetes complications (73) (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc21-S011). In the most recent National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (74) resulted in lower rates of developing retinopathy and nephropathy (75). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (73). In that report, progression from prediabetes to diabetes augmented risk of complications.

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed (57,58). Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur. Based on a population estimate, diabetes in women of childbearing age is underdiagnosed (76). Employing a probabilistic model, Peterson et al. (77) demonstrated cost and health benefits of preconception screening.

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (78). General practice patients between the ages of 40 and 69 years were screened for diabetes and randomly assigned by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (59). The

American Diabetes Association®
Connected *for* Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you? ....

Less than 40 years (0 points)

40–49 years (1 point)

50–59 years (2 points)

60 years or older (3 points)

2. Are you a man or a woman? ....

Man (1 point)   Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?.................

Yes (1 point)   No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? ....

Yes (1 point)   No (0 points)

5. Have you ever been diagnosed with high blood pressure? ....

Yes (1 point)   No (0 points)

6. Are you physically active? ....

Yes (0 points)   No (1 point)

7. What is your weight category? ....

See chart at right.

ADD UP YOUR SCORE.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Diabetes Risk Test | **American Diabetes Association®**

Learn more at **diabetes.org/risktest** | 1-800-DIABETES (800-342-2383)

Figure 2.1—ADA risk test (diabetes.org/socrisktest).

excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes (79); moreover, screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (<$11,000 per quality-adjusted life year gained—2010 modeling data) (80). Cost-effectiveness of

screening has been reinforced in cohort studies (81,82).

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic patients include the following.

Age
Age is a major risk factor for diabetes. Testing should begin at no later than age 45 years for all patients. Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

BMI and Ethnicity
In general, BMI $\geq$25 kg/m^2 is a risk factor for diabetes. However, data suggest that the BMI cut point should be lower for the Asian American population (83,84). The BMI cut points fall consistently between 23 and 24 kg/m^2 (sensitivity of 80%) for nearly all Asian American subgroups (with levels slightly lower for Japanese Americans). This makes a rounded cut point of 23 kg/m^2 practical. An argument can be made to push the BMI cut point to lower than 23 kg/m^2 in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from WHO also suggests that a BMI of $\geq$23 kg/m^2 should be used to define increased risk in Asian Americans (85). The finding that one-third to one-half of diabetes in Asian Americans is undiagnosed suggests that testing is not occurring at lower BMI thresholds (86,87).

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m^2 in non-Hispanic Whites was equivalent to a BMI of 26 kg/m^2 in African Americans (88).

Medications
Certain medications, such as glucocorticoids, thiazide diuretics, some HIV medications (23), and atypical antipsychotics (66), are known to increase the risk of diabetes and should be considered when deciding whether to screen.

HIV
Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies, so a screening protocol is recommended (89). The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring (24). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among patients with HIV and diabetes, preventive health care using an approach used in patients without HIV is critical to reduce the risks of microvascular and macrovascular complications. Diabetes risk is increased with certain PIs and NRTIs. New-onset diabetes is estimated to occur in more than 5% of patients infected with HIV on PIs, whereas more than 15% may have prediabetes (90). 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 patients with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (91). 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, antihyperglycemic agents may still be necessary.

Testing Interval
The appropriate interval between screening tests is not known (92). 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 (92). In especially high-risk individuals, particularly with weight gain, shorter intervals between screening may be useful.

Community Screening
Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. 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 testing 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 (93).

Screening in Dental Practices
Because periodontal disease is associated with 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 (94–96), with one study estimating that 30% of patients $\geq$30 years of age seen in general dental practices had dysglycemia (96,97). A similar study in 1,150 dental patients >40 years old in India reported 20.69% and 14.60% meeting criteria for prediabetes and diabetes using random blood glucose. Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents
In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in racial and ethnic minority populations (53). See **Table 2.4** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (25). See **Table 2.2** and **Table 2.5** for the criteria for the diagnosis of diabetes and prediabetes, respectively, which apply to children, adolescents, and adults. See Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013) for additional information on type 2 diabetes in children and adolescents.

Some studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (98). However, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (99). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes and only A1C assays without

interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this cohort to decrease barriers to screening (100,101).

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

2.15 Annual screening for cystic fibrosis–related diabetes (CFRD) with an oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with CFRD. **B**

2.16 A1C is not recommended as a screening test for cystic fibrosis–related diabetes. **B**

2.17 Patients with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. **A**

2.18 Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (102). Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test; however, recent publications suggest that an A1C cut point threshold of 5.5% (5.8% in a second

study) would detect more than 90% of cases and reduce patient screening burden (103,104). Ongoing studies are underway to validate this approach. Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (103,104). The Cystic Fibrosis Foundation Patient Registry (105) evaluated 3,553 cystic fibrosis patients and diagnosed 445 (13%) with CFRD. Early diagnosis and treatment of CFRD was associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (increased 10% per decade), genotype, decreased lung function, and female sex (106,107). Continuous glucose monitoring or HOMA of β-cell function (108) may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside of the research setting (109).

CFRD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (110). There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in cystic fibrosis patients with diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and patients gained 0.39 ($\pm$ 0.21) BMI units ($P = 0.02$). The repaglinide-treated group had initial weight gain, but this was not sustained by 6 months. The placebo group continued to lose weight (110). Insulin remains the most widely used therapy for CFRD (111). The primary rationale for the use of insulin in patients with CFRD is to induce an anabolic state while promoting macronutrient retention and weight gain.

Additional resources for the clinical management of CFRD can be found in the position statement "Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes: A Position Statement of the American Diabetes Association and a Clinical Practice Guideline of the Cystic Fibrosis Foundation, Endorsed by the Pediatric Endocrine Society" (112) and in the International Society for Pediatric and Adolescent

Diabetes's 2014 clinical practice consensus guidelines (102).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.19 Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of posttransplantation diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection. **B**

2.20 The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. **B**

2.21 Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (113). "New-onset diabetes after transplantation" (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes patients with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (114). Another term, "posttransplantation diabetes mellitus" (PTDM) (114,115), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (114–117). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (117,118). 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 care provider is to treat hyperglycemia appropriately regardless of the type of immunosuppression (114). Risk factors for PTDM include both general diabetes risks (such as age,

family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents (119). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance immunosuppression and in the absence of acute infection (117–120). In a recent study of 152 heart transplant recipients, 38% had PTDM at 1 year. Risk factors for PTDM included elevated BMI, discharge from the hospital on insulin, and glucose values in the 24 h prior to hospital discharge (121). In an Iranian cohort, 19% had PTDM after heart and lung transplant (122). The OGTT is considered the gold standard test for the diagnosis of PTDM (1 year posttransplant) (114,115,123,124). However, screening patients using fasting glucose and/or A1C can identify high-risk patients requiring further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (119,125,126). Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (117,119,127). Insulin therapy is the agent of choice for the management of hyperglycemia, PTDM, and preexisting diabetes and diabetes in the hospital setting. After discharge, patients with preexisting diabetes could go back on their pretransplant regimen if they were in good control before transplantation. Those with previously poor control or with persistent hyperglycemia should continue insulin with frequent home self-monitoring of blood glucose to determine when insulin dose reductions may be needed and when it may be appropriate to switch to noninsulin agents.

No studies to date have established which noninsulin agents are safest or most efficacious in PTDM. The choice of agent is usually made based on the side effect profile of the medication and possible interactions with the patient's immunosuppression regimen (119). Drug dose adjustments may be required because of decreases in the glomerular filtration rate, a relatively common complication in transplant patients. A small short-term pilot study reported that metformin was safe to use in renal transplant recipients (128), but its safety has not been determined in other types of organ transplant. Thiazolidinediones have been used successfully in patients with liver and kidney transplants, but side effects include fluid retention, heart failure, and osteopenia (129, 130). Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials (131,132). Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in patients with PTDM are needed.

MONOGENIC DIABETES SYNDROMES

Recommendations

2.22 All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**

2.23 Children and those diagnosed in early adulthood who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. **A**

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

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). **Table 2.6** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (133).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed "neonatal" or "congenital" diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (134–137). 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. A recent report details a de novo mutation in *EIF2B1* affecting eIF2 signaling associated with permanent neonatal diabetes and hepatic dysfunction, similar to Wolcott-Rallison syndrome but with few severe comorbidities (138). Correct diagnosis has critical implications because most patients with K_{ATP}-related neonatal diabetes will exhibit improved glycemic control when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and, while intensive insulin management is currently the preferred treatment strategy, there are important genetic counseling considerations, as most of the mutations that cause diabetes are dominantly inherited.

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 13 genes on different chromosomes identified to date. The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

For individuals with MODY, the treatment implications are considerable and warrant genetic testing (139,140). Clinically, patients with GCK-MODY exhibit mild, stable fasting hyperglycemia and do not require antihyperglycemic therapy except sometimes during pregnancy. Patients with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy. Mutations or deletions in *HNF1B* are associated with renal cysts

Table 2.6—Most common causes of monogenic diabetes (133)

	Gene	Inheritance	Clinical features
MODY	GCK	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	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]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight 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	KCNJ11	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (PLAGL1, HYMA1)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (138)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy; enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

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.

and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes including PDX1 (IPF1) and NEUROD1.

Diagnosis of Monogenic Diabetes

A diagnosis of one of the three most common forms of MODY, including GCK-MODY, HNF1A-MODY, and HNF4A-MODY, allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members. Genetic screening is increasingly available and cost-effective (138,140).

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, although admittedly "atypical diabetes" is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes (135–137, 139–145). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in patients with monogenic diabetes has been reported (146). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation if available, and consultation is available from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (147), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. A biomarker screening pathway such as the combination of urinary C-peptide/creatinine ratio and antibody screening may aid in determining who should get genetic testing for MODY (148). It is critical to correctly diagnose one of the monogenic forms of diabetes because these patients may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment regimens and delays in diagnosing other family members (149). The correct diagnosis is especially critical for those with GCK-MODY mutations where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (150). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis.

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 (with occasional cases presenting later, mostly INS and ABCC8 mutations) (134,151)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, nonobese, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if nonobese

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

Pancreatic diabetes includes both structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. Hyperglycemia due to general pancreatic dysfunction has been called "type 3c diabetes" and, more recently, diabetes in the context of disease of the exocrine pancreas has been termed pancreoprivic diabetes (1). The diverse set of etiologies includes pancreatitis (acute and chronic), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed elsewhere in this chapter), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders (152), and idiopathic forms (1), which is the preferred terminology. A distinguishing feature is concurrent pancreatic exocrine insufficiency (according to the monoclonal fecal elastase 1 test or direct function tests), pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography), and absence of type 1 diabetes–associated autoimmunity (153–157). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications is similar to other forms of diabetes. In the context of pancreatectomy, islet autotransplantation can be done to retain insulin secretion (158,159). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (160).

GESTATIONAL DIABETES MELLITUS

Recommendations

2.25 Test for undiagnosed prediabetes and diabetes at the first prenatal visit in those with risk factors using standard diagnostic criteria. **B**

2.26 Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously found to have diabetes. **A**

2.27 Test women with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

2.28 Women with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**

2.29 Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

Definition

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy (60), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations (161). First, the best available evidence reveals that many, perhaps most, cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant women of reproductive age. It is the severity of hyperglycemia that is clinically important with regard to both short- and long-term maternal and fetal risks. Universal preconception and/or first trimester screening is hampered by lack of data and consensus regarding appropriate diagnostic thresholds and outcomes and cost-effectiveness (162,163). A compelling argument for further work in this area is the fact that hyperglycemia that would be diagnostic of diabetes outside of pregnancy and is present at the time of conception is associated with an increased risk of congenital malformations that is not seen with lower glucose levels (164,165).

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of reproductive age, with an increase in the number of pregnant women with undiagnosed type 2 diabetes in early pregnancy (166–169). Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes (170) (**Table 2.3**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.2**). Women found to have diabetes by the standard diagnostic criteria used outside of pregnancy should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly. Women who meet the lower glycemic criteria for GDM should be diagnosed with that condition and managed accordingly. Other women should be rescreened for GDM between 24 and 28 weeks of gestation (see Section 14 "Management of Diabetes in Pregnancy," https://doi.org/10.2337/dc21-S014). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT as well as the GDM screening and diagnostic criteria used in the two-step approach were not derived from data in the first half of pregnancy, so the diagnosis of GDM in early pregnancy by either FPG or OGTT values is not evidence based (171) and further work is needed.

GDM is often indicative of underlying β-cell dysfunction (172), which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery (173,174). As effective prevention interventions are available (175,176), women diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time (177).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (178), a large-scale multinational cohort study completed by more than 23,000 pregnant women, 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 2.7**) 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 and Coustan's interpretation of the older O'Sullivan (179) criteria.

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

One-Step Strategy

The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in women at 24–28 weeks of gestation who participated in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis (180). Many regional studies have investigated the impact of adopting the IADPSG criteria on prevalence and have seen a roughly one- to threefold increase (181). The anticipated increase in the incidence of GDM could have a substantial impact on costs and medical infrastructure needs and has the potential to "medicalize" pregnancies previously categorized as normal. A recent follow-up study of women participating in a blinded study of pregnancy OGTTs found that 11 years after their pregnancies, women who would have been diagnosed with GDM by the one-step approach, as compared with those without, 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 larger group of women identified by the one-step approach would benefit from increased screening for diabetes and prediabetes that would accompany a history of GDM (182,183). The ADA recommends the IADPSG diagnostic criteria with the intent of optimizing gestational outcomes because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits of using IADPSG to the offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria. Those trials found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (184,185). It is important to note that 80–90% of women being treated for mild GDM in these two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped with the thresholds recommended by the IADPSG, and in one trial (185), 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 randomized controlled trials of treating versus not treating GDM diagnosed by the IADPSG criteria but not the Carpenter-Coustan criteria have been published to date. Data are also lacking on how the treatment of lower levels of hyperglycemia affects a mother's future risk for the development of type 2 diabetes and her offspring's risk for obesity, diabetes, and other metabolic disorders. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of women with GDM diagnosed by the one-step strategy (186,187).

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (188). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g glucose load 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 (189). A systematic review for the U.S. Preventive Services Task Force compared GLT cutoffs of 130 mg/dL (7.2 mmol/L) and 140 mg/dL (7.8 mmol/L) (190). The higher cutoff yielded sensitivity of 70–88% and specificity of 69–89%, while the lower cutoff was 88–99% sensitive and 66–77% specific. Data regarding a cutoff of 135 mg/dL are limited. As for other screening tests, choice of a cutoff is based upon the trade-off between sensitivity and specificity. The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (191).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating

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Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women 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 women 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 patient 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 [193]):
- 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 notes that one elevated value can be used for diagnosis (189).

the benefits of the one-step strategy and the potential negative consequences of identifying a large group of women 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 is therefore easier to accomplish for many women. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (192), 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 (189). If this approach is implemented, the incidence of GDM by the two-step strategy 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 (193,194). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan (179), 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 (195) demonstrated that treatment was similarly beneficial in patients meeting only the lower thresholds per Carpenter-Coustan (193) and in those meeting only the higher thresholds per National Diabetes Data Group (194). 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 2.7**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A cost-benefit estimation comparing the two strategies concluded that the one-step approach is cost-effective only if patients with GDM receive postdelivery counseling and care to prevent type 2 diabetes (196). 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).

As the IADPSG criteria ("one-step strategy") have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (197), and IADPSG may be the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (198,199). In addition, 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 (200,201). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policy makers. Longer-term outcome studies are currently underway.

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