



American Diabetes Association

## 2. Classification and Diagnosis of Diabetes

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### CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to  $\beta$ -cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of insulin secretion on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation)

*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 cohorts. Occasionally, patients with type 2 diabetes may present with diabetic ketoacidosis (DKA). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and approximately one-third with DKA (2). The onset of type 1 diabetes may be more variable in adults, and they may not present with the classic symptoms seen in children. Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the true diagnosis becomes more obvious over time.

### DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on the **plasma glucose criteria**, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) or the **A1C criteria** (1,3) (**Table 2.1**).

The same tests are used to screen for and diagnose diabetes and to detect individuals with prediabetes. 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 2.1**). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Numerous studies have confirmed that, compared with FPG cut points and A1C, the 2-h PG value diagnoses more people with diabetes.

#### A1C

The A1C test should be performed using a method that is certified by the NGSP ([www.ngsp.org](http://www.ngsp.org)) and standardized or traceable to the Diabetes Control and

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**Table 2.1—Criteria for the diagnosis of diabetes**FPG  $\geq 126$  mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.\*

OR

2-h PG  $\geq 200$  mg/dL (11.1 mmol/L) during an 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

A1C  $\geq 6.5\%$  (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  $\geq 200$  mg/dL (11.1 mmol/L).

\*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Complications Trial (DCCT) reference assay. Although point-of-care A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of point-of-care assays for diagnostic purposes is not recommended.

The A1C has several advantages compared with the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and 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. National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of  $\geq 6.5\%$  (48 mmol/mol) identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of  $\geq 126$  mg/dL (7.0 mmol/L) (4).

It is important to take age, race/ethnicity, and anemia/hemoglobinopathies into consideration when using the A1C to diagnose diabetes.

#### Age

The epidemiological studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations. Therefore, it remains unclear if A1C and the same A1C cut point should be used to diagnose diabetes in children and adolescents (4,5).

#### Race/Ethnicity

A1C levels may vary with patients' race/ethnicity (6,7). For example, African Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and postglucose load glucose levels. African Americans 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 (8). Moreover, the association of A1C with risk for complications is similar in African Americans and non-Hispanic whites (9).

#### Hemoglobinopathies/Anemias

Interpreting A1C levels in the presence of certain hemoglobinopathies and anemia may be problematic. For patients with an abnormal hemoglobin but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used. An updated list of interferences is available at [www.ngsp.org/interf.asp](http://www.ngsp.org/interf.asp).

#### Red Blood Cell Turnover

In conditions associated with increased red blood cell turnover, such as pregnancy (second and third trimesters), recent blood loss or transfusion, erythropoietin therapy, or hemolysis, only blood glucose criteria should be used to diagnose diabetes.

#### 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  $\geq 200$  mg/dL [11.1 mmol/L]), a second test is required for confirmation. It is recommended that the same test be repeated without delay using a new blood sample for confirmation because there will be a greater likelihood of concurrence. 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, 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. 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  $\geq 6.5\%$  [48 mmol/mol]) but not FPG ( $< 126$  mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Since all the tests have preanalytic and analytic variability, it is possible that an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is least likely for A1C, more likely for FPG, and most likely for the 2-h PG, especially if the glucose samples remain at room temperature and are not centrifuged promptly. Barring laboratory error, such patients will likely have test results near the margins of the diagnostic threshold. The health care professional should follow the patient closely and repeat the test in 3–6 months.

## CATEGORIES OF INCREASED RISK FOR DIABETES (PREDIABETES)

### Recommendations

- Testing to assess risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup> or  $\geq 23$  kg/m<sup>2</sup> in Asian Americans) and who have one or more additional risk factors for diabetes. **B**
- For all patients, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for prediabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. **B**
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. **B**
- Testing to detect prediabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

### Description

In 1997 and 2003, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (10,11) recognized a group of individuals whose glucose

levels did not meet the criteria for diabetes but were too high to be considered normal. “Prediabetes” is the term used for individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and indicates an increased risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes (Table 2.2) and cardiovascular disease (CVD). IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

### Diagnosis

In 1997 and 2003, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (10,11) defined IFG as FPG levels 100–125 mg/dL (5.6–6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels 140–199 mg/dL (7.8–11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous 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 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 an A1C between 5.5–6.0% (37–42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). 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 an A1C of 5.0% (31 mmol/mol) (12). 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 (13). Other analyses suggest that an A1C of 5.7% (39 mmol/mol) is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (14), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (15).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. As with those with IFG and/or IGT, individuals with an 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 4 “Prevention or Delay of Type 2 Diabetes”). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (12). 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 2.3 summarizes the categories of prediabetes and Table 2.2 the criteria for prediabetes testing. For recommendations regarding risk factors and screening for prediabetes, see pp. S17–S18 (“Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults” and “Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents”).

### TYPE 1 DIABETES

#### Recommendations

- Blood glucose rather than A1C should be used to diagnose acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia. **E**
- Inform the relatives of patients with type 1 diabetes of the opportunity to be tested for type 1 diabetes risk, but only in the setting of a clinical research study. **E**

#### Diagnosis

In a patient with acute symptoms, measurement of blood glucose is part of the definition of diabetes (classic symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose  $\geq 200$  mg/dL [11.1 mmol/L]). In these cases, knowing the blood glucose level is critical because, in addition to confirming that symptoms are due to diabetes, this will inform management decisions. Some providers may also want to know the A1C to determine how long a patient has had hyperglycemia.

#### 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  $\beta$ -cells. Autoimmune markers include

islet cell autoantibodies and autoantibodies to insulin, GAD (GAD65), the tyrosine phosphatases IA-2 and IA-2 $\beta$ , and ZnT8. Type 1 diabetes is defined by one 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.

The rate of  $\beta$ -cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient  $\beta$ -cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. 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 commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of  $\beta$ -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 should not preclude the diagnosis. These patients are also prone to other autoimmune disorders such as Hashimoto thyroiditis, celiac disease, Graves disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

#### Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of  $\beta$ -cell autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement

**Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults**

1. Testing should be considered in all adults who are overweight (BMI  $\geq 25$  kg/m<sup>2</sup> or  $\geq 23$  kg/m<sup>2</sup> in Asian Americans) and have additional risk factors:
  - physical inactivity
  - first-degree relative with diabetes
  - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
  - women who delivered a baby weighing  $>9$  lb or were diagnosed with GDM
  - hypertension ( $\geq 140/90$  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
  - A1C  $\geq 5.7\%$  (39 mmol/mol), IGT, or IFG on previous testing
  - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
  - history of CVD
2. For all patients, testing should begin at age 45 years.
3. 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 (e.g., those with prediabetes should be tested yearly) and risk status.

for insulin replacement therapy in affected patients may be intermittent.

**Testing for Type 1 Diabetes Risk**

The incidence and prevalence of type 1 diabetes is increasing (16). 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 ketoacidosis (2). Several studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes (17). Such testing, coupled with education about diabetes symptoms and close follow-up in an observational clinical study, may enable earlier identification of type 1 diabetes onset (18). There is evidence to suggest that early diagnosis may limit acute complications (19).

A recent 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 (19,20). 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.

Although there is currently a lack of accepted screening programs, one should consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study (<http://www2.diabetestrialnet.org>). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. Higher-risk individuals may be tested, but only in the context of a clinical research setting. Individuals who test positive will be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are

**Table 2.3—Categories of increased risk for diabetes (prediabetes)\***

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG in the 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)

\*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.

being conducted to test various methods of preventing type 1 diabetes in those with evidence of autoimmunity ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

**TYPE 2 DIABETES**

**Recommendations**

- Testing to detect type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup> or  $\geq 23$  kg/m<sup>2</sup> in Asian Americans) and who have one or more additional risk factors for diabetes. **B**
- For all patients, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for type 2 diabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. **B**
- In patients with diabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. **B**
- Testing to detect type 2 diabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

**Description**

Type 2 diabetes, previously referred to as “non–insulin-dependent diabetes” or “adult-onset diabetes,” accounts for 90–95% of all diabetes. This form encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. 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  $\beta$ -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 are overweight or obese. Excess weight itself causes some degree of insulin resistance. Patients who are not obese or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

Ketoacidosis seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the

stress of another illness such as infection. 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. Nevertheless, even undiagnosed patients are at increased risk of developing macrovascular and microvascular complications.

Whereas patients with type 2 diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these patients would be expected to result in even higher insulin values had their  $\beta$ -cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal.

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM, in those with hypertension or dyslipidemia, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition, more so than type 1 diabetes. However, the genetics of type 2 diabetes is poorly understood.

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

Prediabetes and type 2 diabetes meet criteria for conditions in which early detection 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 4 "Prevention or Delay of Type 2 Diabetes") and reduce the risk of diabetes complications (see Section 8 "Cardiovascular Disease and Risk Management" and Section 9 "Microvascular Complications and Foot Care").

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed (21). 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.

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (22). General practice patients between the ages of 40–69 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 (22). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to prove that screening and early intensive treatment impact outcomes. Mathematical modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of glycemia and cardiovascular risk factors in type 2 diabetes (23); 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) (24).

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

#### Age

Testing recommendations for diabetes in asymptomatic adults are listed in **Table 2.2**. Age is a major risk factor for diabetes. Testing should begin at age 45 years for all patients.

#### BMI and Ethnicity

Testing should be considered in adults of any age with BMI  $\geq 25$  kg/m<sup>2</sup> and one or more additional risk factors for diabetes. However, recent data (25) and evidence from the ADA position statement "BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening" (26) suggest that the BMI cut point should be lower for the Asian American population. For diabetes screening purposes, the BMI cut points fall consistently between 23 and 24 kg/m<sup>2</sup>

(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<sup>2</sup> practical. In determining a single BMI cut point, it is important to balance sensitivity and specificity so as to provide a valuable screening tool without numerous false positives. An argument can be made to push the BMI cut point to lower than 23 kg/m<sup>2</sup> in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from the WHO also suggest that a BMI  $\geq 23$  kg/m<sup>2</sup> should be used to define increased risk in Asian Americans (27). The finding that half of diabetes in Asian Americans is undiagnosed suggests that testing is not occurring at lower BMI thresholds (21).

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<sup>2</sup> in non-Hispanic whites was equivalent to a BMI of 26 kg/m<sup>2</sup> in African Americans (28).

#### Medications

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (29), are known to increase the risk of diabetes and should be considered when ascertaining a diagnosis.

#### Diagnostic Tests

*FPG, 2-h PG after 75-g OGTT, and A1C are equally appropriate for testing.* 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 (30,31) has primarily been demonstrated among individuals with IGT, not for individuals with isolated IFG or for those with prediabetes defined by A1C criteria.

#### Testing Interval

The appropriate interval between tests is not known (32). 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 (32).

#### Community Screening

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

Community testing outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. 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.

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

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in ethnic populations (16). Recent studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (33). 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 (34). 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 (35,36). The modified recommendations of the ADA consensus report "Type 2 Diabetes in Children and Adolescents" are summarized in **Table 2.4**.

### GESTATIONAL DIABETES MELLITUS

#### Recommendations

- Test for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. **B**
- Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously known to have diabetes. **A**
- Screen women with gestational diabetes mellitus for persistent diabetes at 6–12 weeks postpartum,

using the oral glucose tolerance test and clinically appropriate non-pregnancy diagnostic criteria. **E**

- 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**
- Women with a history of gestational diabetes mellitus found to have prediabetes should receive lifestyle interventions 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 (10), regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but it was limited by imprecision.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, with an increase in the number of pregnant women with undiagnosed type 2 diabetes (37). 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 (**Table 2.2**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.1**). Women with diabetes in the first trimester would be classified as having type 2 diabetes. GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes (see Section 12 "Management of Diabetes in Pregnancy").

#### Diagnosis

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (38), a large-scale (25,000 pregnant women) multinational cohort study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, 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 2.5**) can be accomplished with either of two strategies:

1. "One-step" 75-g OGTT or
2. "Two-step" approach with a 50-g (non-fasting) screen followed by a 100-g OGTT for those who screen positive

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

In the 2011 Standards of Care (39), the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (40). The IADPSG defined diagnostic cut points for GDM as the average glucose values (fasting, 1-h, and 2-h PG) in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean glucose 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. The ADA recognized that the anticipated increase in the incidence of GDM would have significant impact on the costs, medical infrastructure capacity, and potential for increased "medicalization" of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their offspring.

The expected benefits to these pregnancies and offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (41,42). It is important to note that 80–90% of women being treated for mild GDM in two randomized controlled trials (whose glucose values overlapped with the thresholds recommended by the IADPSG) could be managed with lifestyle therapy alone. Data are lacking on how the

**Table 2.4—Testing for type 2 diabetes or prediabetes in asymptomatic children\***

## Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

## Plus any two of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
- Maternal history of diabetes or GDM during the child's gestation

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

\*Persons aged ≤18 years.

treatment of lower levels of hyperglycemia affects a mother's risk for the development of type 2 diabetes in the future and her offspring's risk for obesity, diabetes, and other metabolic dysfunction. 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.

**Two-Step Strategy**

In 2013, the National Institutes of Health (NIH) convened a consensus development conference on diagnosing GDM. The 15-member panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields to consider diagnostic criteria (43). The panel recommended the two-step approach of screening with a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive, a strategy commonly used in the U.S.

Key factors reported in the NIH panel's decision-making process were the lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM, including medicalization of pregnancy with increased interventions 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 (44), and shoulder dystocia, without increasing small-for-gestational-age births. The American College of Obstetricians and Gynecologists (ACOG) updated

its guidelines in 2013 and supported the two-step approach (45).

**Future Considerations**

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. 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., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (46) and may be the preferred approach. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria (47). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently under way.

**MONOGENIC DIABETES SYNDROMES****Recommendations**

- All children diagnosed with diabetes in the first 6 months of life should have genetic testing. **B**
- Maturity-onset diabetes of the young should be considered in individuals who have mild stable fasting hyperglycemia and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes. **E**

- Because a diagnosis of maturity-onset diabetes of the young may impact therapy and lead to identification of other affected family members, consider referring individuals with diabetes not typical of type 1 or type 2 diabetes and occurring in successive generations (suggestive of an autosomal dominant pattern of inheritance) to a specialist for further evaluation. **E**

Monogenic defects that cause  $\beta$ -cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years).

**Neonatal Diabetes**

Neonatal diabetes is a monogenic form of diabetes with onset in the first 6 months of life. It can be mistaken for the more common type 1 diabetes, but type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. The most common genetic defect causing transient disease is a defect on ZAC/HYAMI imprinting, whereas permanent neonatal diabetes is most commonly an autosomal dominant defect in the gene encoding the Kir6.2 subunit of the  $\beta$ -cell  $K_{ATP}$  channel. Correct diagnosis has important implications, because children with neonatal diabetes due to mutations affecting Kir6.2 should be treated with sulfonylureas rather than insulin.

**Maturity-Onset Diabetes of the Young**

MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action. It is inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form (MODY 3) is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1 $\alpha$  and also referred to as transcription factor-1 (TCF-1). The second most common form (MODY 2) is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the  $\beta$ -cell. The less common forms of MODY result from mutations in other

**Table 2.5—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 overt 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 overt diabetes.

If the plasma glucose level measured 1 h after the load is  $\geq 140$  mg/dL\* (7.8 mmol/L), 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 if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (55)	or	NDDG (56)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. \*The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

transcription factors, including HNF-4 $\alpha$ , HNF-1 $\beta$ , insulin promoter factor-1 (IPF-1), and NeuroD1.

**Diagnosis**

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. These individuals should be referred to a specialist for further evaluation. Readily available commercial genetic testing now enables a genetic diagnosis. It is important 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 treatment regimens and delays in diagnosing other family members (48,49).

The diagnosis of monogenic diabetes should be considered in children with the following findings:

- Diabetes diagnosed within the first 6 months of life
- Strong family history of diabetes but without typical features of type 2 diabetes (nonobese, low-risk ethnic group)
- Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and nonobese
- Diabetes with negative diabetes-associated autoantibodies and

without typical clinical features of type 2 diabetes

**CYSTIC FIBROSIS–RELATED DIABETES****Recommendations**

- Annual screening for cystic fibrosis–related diabetes with oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis who do not have cystic fibrosis–related diabetes. **B**
- A1C as a screening test for cystic fibrosis–related diabetes is not recommended. **B**
- Patients with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. **A**
- In patients with cystic fibrosis and impaired glucose tolerance without confirmed diabetes, prandial insulin therapy should be considered to maintain weight. **B**
- 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. 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  $\beta$ -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. 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. Continuous glucose monitoring may be more sensitive than OGTT to detect risk for progression to CFRD, but evidence linking continuous glucose monitoring results to long-term outcomes is lacking and its use is not recommended for screening (50).

CFRD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (51). 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 (52). Insulin remains the most widely used therapy for CFRD (53).

Recommendations for the clinical management of CFRD can be found in the ADA 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” (54).



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