# 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

*Diabetes Care 2025;48(Suppl. 1):S27–S49 | https://doi.org/10.2337/dc25-S002*

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

## DIAGNOSTIC TESTS FOR DIABETES

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

***Recommendations***

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

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

### Screening and Diagnosis of Diabetes

FPG, 2-h PG during 75-g OGTT, and A1C are appropriate for screening and diagnosis. It should be noted that detection rates of different screening tests vary in both

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

*Duality of interest information for each author is available at https://doi.org/10.2337/dc25-SDIS.*

*Suggested citation: American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of Care in Diabetes—2025. Diabetes Care 2025;48(Suppl. 1): S27–S49*

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

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

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

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

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

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

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

An advantage of glucose testing is that these assays are inexpensive and widely available. Disadvantages include the high diurnal variation in glucose and fasting requirement. Individuals may have difficulty fasting for the full 8-h period or may misreport their fasting status (**Table 2.3**). Recent physical activity, illness, or acute stress can affect glucose concentrations. Glycolysis is also an important and underrecognized concern with glucose testing. Glucose concentrations will be falsely low if samples are not handled properly and promptly prior to analysis (1).

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

**Table 2.2—Criteria defining prediabetes in nonpregnant individuals**

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

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

### Use of A1C for Screening and Diagnosis of Diabetes

***Recommendations***

**2.2a** The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) as

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

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

Data are from Selvin (217).

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

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

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

**2.4** In conditions associated with an altered relationship between A1C and glycemia, such as some hemoglobin variants, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, hemolysis, or erythropoietin therapy, plasma glucose criteria should be used to diagnose diabetes. **B**

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

Point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic management in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)–regulated and CLIA-waived settings. FDA-approved point-of-care A1C testing can be used in laboratories or sites that are CLIA certified, are inspected, and meet the CLIA quality standards. These standards include specified personnel requirements (including documented annual competency assessments) and participation three times per year in an approved proficiency testing program (15–18).

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

A1C reflects glucose bound to hemoglobin over the life span of the erythrocyte (~120 days) and is thus a "weighted" average that is more heavily affected by recent blood glucose exposure. This means that clinically meaningful changes in A1C can be seen in <120 days. A1C is an indirect measure of glucose exposure, and factors that affect hemoglobin concentrations or erythrocyte turnover can affect A1C

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(e.g., thalassemia or folate deficiency) (**Table 2.3**). A1C may not be a suitable diagnostic test in people with anemia, people treated with erythropoietin, or people undergoing hemodialysis or HIV treatment (1,19,20). Some hemoglobin variants can interfere with A1C test results, but this depends on the specific assay. For individuals 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 ngsp.org/interf.asp. Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals in the U.S., is associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with levels in individuals without the variant (21).

There is controversy regarding racial differences in A1C. Studies have found that African American individuals have slightly higher A1C levels than non-Hispanic White or Hispanic people (22–25). The glucose-independent racial difference in A1C is small (~0.3 percentage points) and may reflect genetic differences in hemoglobin or red cell turnover that vary by ancestry. There is an emerging understanding of the genetic determinants of A1C (21), but the field lacks adequate genetic data in diverse populations (26,27). While some genetic variants might be more common in certain race or ancestry groups, it is important that we do not use race or ancestry as proxies for poorly understood genetic differences. Reassuringly, studies have shown that the association of A1C with risk for complications appears to be similar in African American and non-Hispanic White populations (28).

### Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., individual with classic symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]), confirmation is necessary to establish the diagnosis. This can be accomplished by two abnormal screening test results, measured either at the same time (29) or at two different time points. If using samples at two different time points, it is recommended that the second test, which may be either a repeat of the initial test or a different test, be performed in a timely manner. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. Two different tests (such as A1C and FPG) both having results above the diagnostic threshold when collected at the same time or at two different time points would also confirm the diagnosis. On the other hand, if an individual has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of factors that may affect measured A1C or glucose levels. The diagnosis is made based on the confirmatory screening test. For example, if an individual meets the diabetes criterion of 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.

If individuals have test results near the margins of the diagnostic threshold, the health care professional should educate the individual about the onset of possible hyperglycemic symptoms and repeat the test in 3–6 months.

Consistent and substantial discordance between glucose values and A1C test results should prompt additional follow-up to determine the underlying reason for the discrepancy (including evaluation for the possibility of a problem or interference with either test) and whether it has clinical implications for the individual (**Table 2.3**). In addition, consider other biomarkers, such as fructosamine and glycated albumin, which are alternative measures of chronic hyperglycemia that are approved for clinical use for monitoring glycemic management in people with diabetes.

## CLASSIFICATION

***Recommendation***

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

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

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

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining personalized therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes having onset only in adults and type 1 diabetes having onset only in children are not accurate, as both diseases occur in all age-groups. Children with type 1 diabetes often present with the hallmark symptoms of polyuria/polydipsia, and approximately half present with DKA (30–32). 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 progress to insulin replacement more slowly (33–35). The features most useful in determination of type 1 diabetes include younger age at diagnosis (<35 years) with lower BMI (<25 kg/m$^2$), unintentional weight loss, ketoacidosis, and plasma glucose >360 mg/dL (>20 mmol/L) at presentation (36) (**Fig. 2.1**). Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases, are weak discriminators. Occasionally, people with type 2 diabetes may present with DKA (37), particularly members of certain racial, ethnic, and ancestral groups (e.g., African American and Hispanic/Latino

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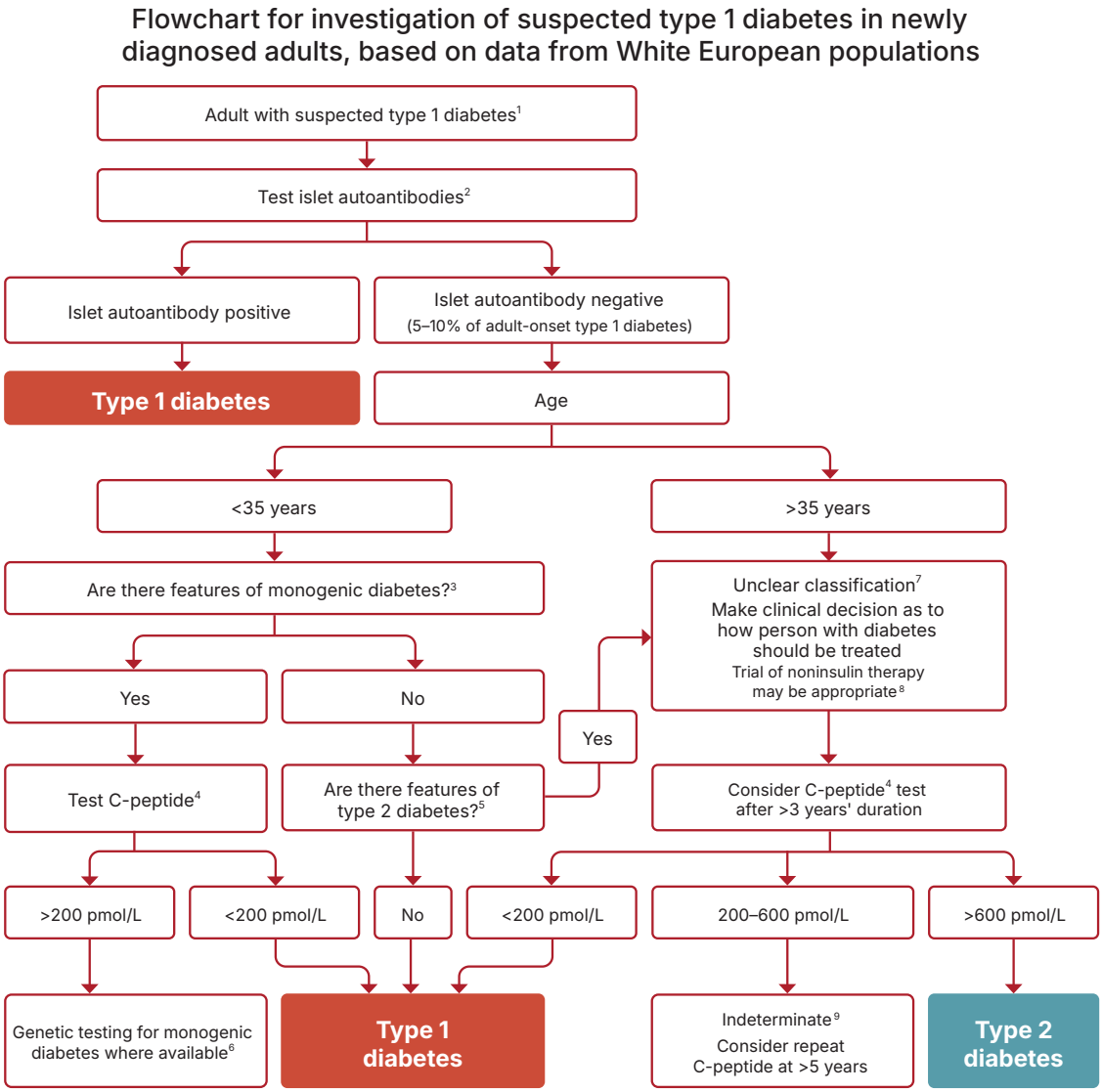



**Figure 2.1**—Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations. [1]No single clinical feature confirms type 1 diabetes in isolation. [2]Glutamic acid decarboxylase (GAD) should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA-2) and/or zinc transporter 8 (ZnT8) where these tests are available. In individuals who have not been treated with insulin, antibodies against insulin may also be useful. In those diagnosed at <35 years of age who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes, since 5–10% of people with type 1 diabetes do not have antibodies. [3]Monogenic diabetes is suggested by the presence of one or more of the following features: A1C <58 mmol/mol (<7.5%) at diagnosis, one parent with diabetes, features of a specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, and severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model probability >5% (diabetesgenes.org/exeter-diabetes-app/ModyCalculator). [4]A C-peptide test is only indicated in people receiving insulin treatment. A random sample (with concurrent glucose) within 5 h of eating can replace a formal C-peptide stimulation test in the context of classification. If the result is ≥600 pmol/L (≥1.8 ng/mL), the circumstances of testing do not matter. If the result is <600 pmol/L (<1.8 ng/mL) and the concurrent glucose is <4 mmol/L (<70 mg/dL) or the person may have been fasting, consider repeating the test. Results showing very low levels (e.g., <80 pmol/L [<0.24 ng/mL]) do not need to be repeated. Where a person is insulin treated, C-peptide must be measured prior to insulin discontinuation to exclude severe insulin deficiency. Do not test C-peptide within 2 weeks of a hyperglycemic emergency. [5]Features of type 2 diabetes include increased BMI (≥25 kg/m$^2$), absence of weight loss, absence of ketoacidosis, and less marked hyperglycemia. Less discriminatory features include non-White ethnicity, family history, longer duration and milder severity of symptoms prior to presentation, features of metabolic syndrome, and absence of a family history of autoimmunity. [6]If genetic testing does not confirm monogenic diabetes, the classification is unclear and a clinical decision should be made about treatment. [7]Type 2 diabetes should be strongly considered in older individuals. In some cases, investigation for pancreatic or other types of diabetes may be appropriate. [8]A person with possible type 1 diabetes who is not treated with insulin will require careful monitoring and education so that insulin can be rapidly initiated in the event of glycemic deterioration. [9]C-peptide values 200–600 pmol/L (0.6–1.8 ng/mL) are usually consistent with type 1 diabetes or maturity-onset diabetes of the young but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low BMI or after long duration. Reprinted and adapted from Holt et al. (36).

adults), who may present with ketosis-prone type 2 diabetes (30). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent. It is important for health care professionals to realize that classification of diabetes type is not always straightforward at presentation

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and that misdiagnosis is common and can occur in ~40% of adults with new type 1 diabetes (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes). In comparison, individuals with maturity-onset diabetes of the young (MODY) may be misdiagnosed as having type 1 diabetes (36). Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the diagnosis generally becomes more obvious over time in people with β-cell deficiency as the degree of β-cell deficiency becomes clear (**Fig. 2.1**). One useful clinical tool for distinguishing diabetes type is the **AABBCC** approach: **A**ge (e.g., for individuals <35 years old, consider type 1 diabetes); **A**utoimmunity (e.g., personal or family history of autoimmune disease or polyglandular autoimmune syndromes); **B**ody habitus (e.g., BMI <25 kg/m$^2$); **B**ackground (e.g., family history of type 1 diabetes); **C**ontrol (preferred term is "goal," i.e., the inability to achieve glycemic goals on noninsulin therapies); and **C**omorbidities (e.g., treatment with immune checkpoint inhibitors for cancer can cause acute autoimmune type 1 diabetes) (36).

In both type 1 and type 2 diabetes, genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β-cell demise or dysfunction (38). Across the globe, many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing personalized treatment approaches (39). A diagnosis of type 1 diabetes does not preclude also having features classically associated with type 2 diabetes (e.g., insulin resistance, obesity, and other metabolic abnormalities), and until more precise subsets are used in clinical practice, it may be appropriate to categorize such an individual as having features of both type 1 and type 2 diabetes to facilitate access to appropriate treatment (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] or sodium–glucose cotransporter 2 [SGLT2] inhibitor therapies for potential weight and other cardiometabolic benefits) and monitoring systems.

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is clear from prospective studies that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes (40). In at-risk cohorts followed from birth or a very young age, seroconversion rarely occurs before 6 months of age and there is a peak in seroconversion between 9 and 24 months of age (41–43). The rate of progression is dependent on the age at first detection of an autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels may rise well before the clinical onset of diabetes (e.g., changes in FPG and 2-h PG can occur about 6 months before diagnosis) (44), making diagnosis feasible under ideal situations of serial monitoring of individuals at high risk of type 1 diabetes before the onset of DKA. Three distinct stages of type 1 diabetes have been defined (**Table 2.4**) and serve as a framework for research and regulatory decision-making (38,45).

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 with detection of LADA is awareness that slow autoimmune β-cell destruction can occur in adults, leading to a long duration of marginal insulin secretory capacity. For this classification, all forms of diabetes mediated by autoimmune β-cell destruction independent of age of onset are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to have progressive autoimmune β-cell destruction (46), thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA (34,47). At the same time, there is evidence that application of only a single imperfect autoantibody test for determining LADA classification may lead to misclassification of some individuals with type 2 diabetes. Diagnostic accuracy may be improved by using higher-specificity tests, using confirmatory testing for other autoantibodies, and restricting testing to those with clinical features suggestive of autoimmune diabetes (48).

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 genetic predisposition, epigenetic changes, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (38,49–52).

## TYPE 1 DIABETES

***Recommendations***

**2.6** Screening for presymptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), or zinc transporter 8 (ZnT8). **B**

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

**2.8** Having multiple confirmed islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk (**Table 2.4**). When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes should be considered. **B**

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

### Immune-Mediated Diabetes

Autoimmune type 1 diabetes accounts for 5–10% of diabetes and is caused by

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**Table 2.4—Staging of type 1 diabetes**

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

Adapted from Skyler et al. (38). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (84). Dysglycemia can be defined by one or more criteria as outlined in the table.

autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase (GAD) (such as GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8). Numerous clinical studies are being conducted to test various methods of preventing or delaying type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies) (40–42, 47,53,54). The disease has strong HLA associations, with linkage to the *DQB1* and *DRB1* haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing (e.g., DRB1*0301-DQB1*0201 [DR3-DQ2] and DRB1*0401-DQB1*0302 [DR4-DQ8]) or protective (e.g., DRB1*1501 and DQA1*0102-DQB1*0602). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoantibodies and normoglycemia (**Table 2.4**). At stage 1, the 5-year risk of developing symptomatic type 1 diabetes is ∼44% overall but varies considerably based on number, titer, and specificity of autoantibodies as well as age of seroconversion and genetic risk (45). Stage 2 includes individuals with multiple islet autoantibodies and dysglycemia not yet diagnostic of diabetes (dysglycemia can be defined by one or more criteria as outlined in **Table 2.4**). At stage 2 of the disease, there is ∼60% risk by 2 years and ∼75% risk within 5 years of developing a clinical diagnosis of type 1 diabetes (55,56). A consensus guidance provides expert recommendations on what should be monitored and how often these factors should be monitored in individuals with presymptomatic type 1 diabetes (57).

The rate of β-cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults) (44,58). Children and adolescents often present with DKA as the first manifestation of the disease, and rates in the U.S. have increased over the past 20 years (30–32). Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission characterized by decreased insulin needs for months or years, eventually become dependent on insulin for survival, and are at risk for DKA (33–35, 59,60). At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age. Autoimmune destruction of β-cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals did not classically have obesity when they presented with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders, such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"). Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (*FOXP3*) gene, and another disorder caused by the autoimmune regulator (*AIRE*) gene mutation (61,62).

Introduction of immunotherapy, specifically checkpoint inhibitors, for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of type 1 diabetes can occur, with DKA and low or undetectable levels of C-peptide as a marker of endogenous β-cell function (63–65). Fewer than half of these individuals have autoantibodies that are seen in type 1 diabetes, supporting alternate pathobiology. This immune-related adverse event occurs in just under 1% of checkpoint inhibitor–treated individuals but most commonly occurs with agents that block the programmed cell death protein 1/programmed cell death ligand 1 pathway alone or in combination with other checkpoint inhibitors (66). To date, the majority of immune checkpoint inhibitor–related cases of type 1 diabetes occur in people with high-risk HLA susceptibility haplotype for type 1 diabetes; however, people with either a neutral or typically protective

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HLA haplotype for type 1 diabetes can also develop checkpoint inhibitor–associated type 1 diabetes (67). To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications or caring for people who have a history of current or past exposure to these agents should be mindful of this adverse effect and educate and monitor individuals appropriately.

A number of viruses have been associated with type 1 diabetes, including enteroviruses such as Coxsackievirus B. During the coronavirus disease 2019 (COVID-19) pandemic, numbers of cases of hyperglycemia, DKA, and new diabetes increased, suggesting that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a trigger for or can unmask type 1 diabetes (68). Possible mechanisms of β-cell damage include virus-triggered β-cell death, immune-mediated loss of pancreatic β-cells, and damage to β-cells because of infection of surrounding exocrine cells. The cytokine storm associated with COVID-19 infection is a highly inflammatory state that could also contribute. To better characterize and understand the pathogenesis of new-onset COVID-19–related diabetes, a global registry, CoviDIAB, has been established (69).

### Idiopathic Type 1 Diabetes

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

### Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes are increasing (70). People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 25–50% are diagnosed with life-threatening DKA (30–32). Family history of type 1 diabetes increases the risk of developing type 1 diabetes compared with the general population, but the majority, ∼90%, of individuals who develop type 1 diabetes do not have a known relative with the disease. Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes (45), in children from the general population (71,72), or in children from the general population with high genetic risk (73) can identify many individuals who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (40). 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 (53,74,75). 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 (76). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and to prevent DKA (77,78). In several cohort studies, up to 50% of children with only a single autoantibody revert to being islet autoantibody negative during follow-up (79,80). Therefore, it is recommended that the first autoantibody-positive test be confirmed with a second test within 3 months, preferably in a laboratory that meets the performance standards set by the Islet Autoantibody Standardization Program (IASP) (57).

Type 1 diabetes genetic risk scores have been used in newborn screening to identify those at risk for future presentation of the disease. In a simulation using one such genetic risk score, the majority of those who would go on to develop type 1 diabetes, >77%, could be identified within just 10% of the general population, identifying a subset who may most benefit from autoantibody testing (81). As many genetic risk studies have been performed in populations of European ancestry and discriminatory ability may differ in those of different ancestry, more large case-control cohorts from non-European populations are still needed (82).

Screening programs are available in Europe (e.g., Fr1da and gppad.org), Australia (e.g., type1screen.org), and the U.S. (e.g., trialnet.org, askhealth.org, and cascadekids.org). General population-based screening programs may offer broader testing where high-quality, validated assays and resources for appropriate follow-up of results are available, with several countries considering making such testing part of standard care. In 2023, Italy introduced nationwide screening for type 1 diabetes and celiac disease in the general population aged 1–17 years (83). Individuals who test autoantibody positive should be provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, and DKA prevention and should be given consideration for referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes (84).

## PREDIABETES AND TYPE 2 DIABETES

***Recommendations***

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

**2.11a** Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors (**Table 2.5**). **B**

**2.11b** For all other people, screening should begin at age 35 years. **B**

**2.11c** In people without prediabetes or diabetes after screening, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain). **C**

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

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

**2.14** Risk-based screening for prediabetes or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever

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

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

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

occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes. (See **Table 2.6** for evidence grading of risk factors.) **B**

**2.15a** Consider screening people for prediabetes or diabetes if they are on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of these conditions. **C**

**2.15b** In people who are prescribed second-generation antipsychotic medications, screen for prediabetes and diabetes at baseline and repeat 12–16 weeks after medication initiation or sooner, if clinically indicated, and annually thereafter. **B**

**2.16** People with HIV should be screened for diabetes and prediabetes with an FPG test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, FPG should be checked annually. **E**

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

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) and who have one or more additional risk factors:
- Maternal history of diabetes or GDM during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- High-risk race, ethnicity, and ancestry (see **Table 2.5**)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, large- or small-for-gestational-age birth weight)

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

## Prediabetes

Prediabetes is the term used for individuals whose glucose or A1C levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism that results in elevated glucose levels (dysglycemia) intermediate between normoglycemia and diabetes (28,85). People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (**Table 2.2**). As prediabetes is an intermediate state between normoglycemia and diabetes, it is a significant risk factor for progression to diabetes as well as cardiovascular disease and several other cardiometabolic outcomes. Criteria for screening for diabetes or prediabetes in asymptomatic adults are outlined in **Table 2.5**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

### *Diagnosis of Prediabetes*

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (78,84) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (10). It should be noted that the World Health Organization and a number of diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L). The ADA also initially endorsed this IFG lower limit in 1997 (10). However, in 2003 the ADA adopted the new range of 100–125 mg/dL (5.6–6.9 mmol/L) to better define IFG so that the population risk of developing diabetes with IFG would be similar to that with IGT (11).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous curvilinear association between A1C and 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

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20 times higher than that with A1C of 5.0% (31 mmol/mol) (86). 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 (87). 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) (88), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (7).

An A1C range of 5.7–6.4% (39–47 mmol/mol) identifies a group of individuals at high risk for diabetes and cardiovascular outcomes. These individuals should be informed of their increased risk for diabetes and cardiovascular disease and counseled about effective strategies to lower their risks (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities"). Similar to glucose measurements, the continuum of risk is continuous and curvilinear: as A1C rises, the diabetes risk rises disproportionately (86). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [>42 mmol/mol] and individuals with both IFG and IGT).

**Table 2.5** outlines the criteria for screening for prediabetes. The ADA risk test is an additional option (i.e., an awareness tool for the layperson and the health care professional) for assessment to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (**Fig. 2.2**) (diabetes.org/diabetes-risk-test). For additional background regarding risk factors and screening for prediabetes, see screening and testing for prediabetes and type 2 diabetes in asymptomatic adults and screening and testing for prediabetes and type 2 diabetes in children and adolescents, below. For details regarding individuals with prediabetes most likely to benefit from a formal behavioral or lifestyle intervention, see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities."

### Type 2 Diabetes

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

There are various causes of type 2 diabetes. Although the specific etiologies are not known, individuals do not have any of the other known causes of diabetes. Most, but not all, people with type 2 diabetes have overweight or obesity. Excess weight itself causes some degree of insulin resistance. Individuals 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, including sites involved in metabolic dysfunction–associated steatotic liver disease (MASLD) and/or ectopic sites (e.g., skeletal muscle).

DKA seldom occurs spontaneously in type 2 diabetes (30); when seen, it usually arises in individuals who are insulinopenic and already treated with insulin (e.g., missed or inadequate doses); in people with ketosis-prone type 2 diabetes; in association with the stress of another illness such as infection (e.g., COVID-19) or myocardial infarction; in association with illicit drug use (e.g., cocaine); in association with certain social determinants of health; or with the use of certain medications such as glucocorticoids, second-generation antipsychotics, or SGLT2 inhibitors (89,90). HHS is more typically associated with type 2 diabetes (existing or new diagnosis) and is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. People with diabetes can also have mixed clinical features of both DKA and HHS (30).

Type 2 diabetes frequently goes undiagnosed for many years, because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the individual to notice the classic diabetes symptoms caused by hyperglycemia, such as dehydration or unintentional weight loss. Nevertheless, even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.

People with type 2 diabetes early in the disease course may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion that is insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive nutritional changes and exercise, newer pharmacological agents (e.g., GLP-1 RAs), or surgical weight loss can lead to diabetes remission (91–94) (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity (95,96). It occurs more frequently in individuals with prediabetes, prior gestational diabetes mellitus, or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial, ethnic, and ancestral subgroups (**Table 2.5**). 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 are poorly understood and under intense investigation in this era of precision medicine (50). The composition of the gut microbiome may also affect the likelihood of developing type 2 diabetes (97). In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing (e.g., GAD autoantibodies) to exclude the diagnosis of type 1 diabetes (36) (**Fig. 2.1**).

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

Screening for prediabetes and type 2 diabetes risk through a targeted assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the ADA risk test (**Fig. 2.2**) (diabetes.org/diabetes-risk-test), is recommended to guide health care professionals on whether performing a diagnostic test (**Table 2.1**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available (98). The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes. It is important to individualize the risk-to-benefit ratio of formal intervention for

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American Diabetes Association®
Connected for Life®

# Are you at risk for type 2 diabetes?

## Diabetes Risk Test

**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.

WRITE YOUR SCORE IN THE BOX.

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, Hispanic/Latino individuals, 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/diabetes-risk-test | 1-800-DIABETES (800-342-2383)

**Figure 2.2**—ADA risk test (diabetes.org/diabetes-risk-test).

people with prediabetes and consider person-centered goals. Risk models have explored the benefit, in general finding higher benefit of intervention in those at highest risk (99) (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities") and reduced risk of diabetes complications (100) (see Section 10, "Cardiovascular Disease and Risk Management," Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and

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Foot Care"). In the National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (101) resulted in lower rates of developing retinopathy and nephropathy (102). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (100). In that report, progression from prediabetes to diabetes augmented risk of complications.

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

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

#### *Age*

Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people (103). Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

#### *Medications*

Certain medications, such as glucocorticoids, statins (104), thiazide diuretics, some HIV medications (19), and second-generation antipsychotic medications (105), should be considered when deciding whether to screen for prediabetes or diabetes, as these medications are known to increase the risks of these conditions.

For example, people taking second-generation antipsychotic medications require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (105). There is a range of effects on metabolic parameters (e.g., hyperglycemia, dyslipidemia, and weight gain) across second-generation antipsychotic medications. People treated with these agents should be screened for prediabetes or diabetes at baseline, rescreened 12–16 weeks after medication initiation, and screened annually thereafter (105). Repeat testing can occur sooner if clinically warranted.

#### *People With HIV*

People with HIV are at higher risk for developing prediabetes and diabetes. In addition, some antiretroviral (ARV) therapies may further increase the risk. Therefore, a screening protocol for prediabetes and type 2 diabetes is recommended (106). As the A1C test may underestimate glycemia in people with HIV, plasma glucose criteria are preferred to diagnose prediabetes and diabetes (20).

Diabetes risk is increased with certain protease inhibitors (PIs) and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). New-onset diabetes is estimated to occur in more than 5% of individuals infected with HIV on PIs, whereas more than 15% may have prediabetes (107). PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (108). 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 (109). 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 (109). In especially high-risk individuals such as those with previous values nearer to the diabetes diagnostic cut point, shorter intervals between screenings may be useful.

#### *Community Screening*

Ideally, screening should be carried out within a health care setting (including appropriately resourced pharmacies) because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (110).

#### *Screening in Dental Practices*

Because of the bidirectional relationship between periodontal disease and diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (111,112). For example, one study estimated that 30% of individuals ≥30 years of age seen in general dental practices (including both people with and without periodontal disease) had newly diagnosed dysglycemia (112). Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting. For additional background on oral health in relation to prediabetes and type 2 diabetes, see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities."

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

The epidemiologic studies that formed the basis for the recommendations to use A1C and plasma glucose criteria to diagnose prediabetes and diabetes included only adult populations (113). However, ADA clinical guidance concluded that A1C, FPG, or 2-h PG also could be used to test for prediabetes or type 2 diabetes in children and adolescents (114).

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in certain high-risk racial, ethnic, and ancestral subgroups (115). See **Table 2.6** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (114). See **Table 2.1** and **Table 2.2** for the criteria for the diagnosis of diabetes and prediabetes, respectively, that apply to children, adolescents, and adults. See Section 14, "Children and Adolescents," for

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additional information on type 2 diabetes in children and adolescents.

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

***Recommendation***

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

Pancreatic diabetes (also termed pancreatogenic diabetes or type 3c diabetes) includes both structural (e.g., destruction or removal of normal pancreatic tissue) and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. The diverse set of etiologies includes pancreatitis (acute and chronic pancreatic inflammation and associated fibrosis leading to loss of functional exocrine and endocrine pancreatic function), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed later in this section), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders, and idiopathic forms (2); as such, pancreatic diabetes is the preferred umbrella term (116).

Acute (even a single bout) and chronic pancreatitis can lead to postpancreatitis diabetes mellitus (117). A distinguishing feature is concurrent pancreatic exocrine insufficiency (consider screening individuals with acute and chronic pancreatitis for exocrine pancreatic insufficiency by measuring fecal elastase), pathological pancreatic imaging (endoscopic ultrasound, MRI, and computed tomography), and absence of type 1 diabetes–associated autoimmunity (118–122). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications appears to be similar to that of other forms of diabetes.

For people with pancreatitis and diabetes, therapy should be advanced if A1C goals are not met. Glucose-lowering therapies potentially associated with increased risk of pancreatitis (i.e., incretin-based therapies) should be avoided. Early initiation of insulin therapy should be considered. In the context of pancreatectomy, islet autotransplantation can be considered for selected individuals with medically refractory chronic pancreatitis in specialized centers to preserve endogenous islet function and insulin secretion (123,124). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (125).

### Cystic Fibrosis–Related Diabetes

***Recommendations***

**2.18** Annual screening for cystic fibrosis–related diabetes (CFRD) with an OGTT should begin by age 10 years in all people with cystic fibrosis not previously diagnosed with CFRD. **B**

**2.19** A1C is not recommended as a screening test for CFRD due to low sensitivity. However, a value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD. **B**

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

Cystic fibrosis is a multisystem condition arising from recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Pancreatic exocrine damage, which can begin as early as infancy, ultimately leads to pancreatic exocrine insufficiency (126). Cystic fibrosis–related diabetes (CFRD) is a common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (127). The relevance of CFRD is highlighted by its association with increased morbidity, mortality, and patient burden. 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 for CFRD. Not unexpectedly, annual OGTTs are perceived as burdensome, and engagement in current CFRD screening guidelines is poor, with only 30% of adults with cystic fibrosis having annual OGTTs (128). A1C is not recommended for screening due to low sensitivity; however, a value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD and reduces patient screening burden (129–131). Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (129,130). The Cystic Fibrosis Foundation Patient Registry (132) evaluated 3,553 people with cystic fibrosis and identified 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 (10% increase per decade), genotype, decreased lung function, and female sex (133). CGM or HOMA of β-cell function (134) 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 the research setting (127). There is inadequate evidence presently to alter CFRD screening based on use of highly effective CFTR modulator therapy, which uses small-molecule compounds that directly correct the basic defect of the CFTR channel and restore channel function (127).

CFRD mortality has significantly decreased over time, and the gap in mortality between people with cystic fibrosis with and without diabetes has considerably narrowed (135). There are limited clinical trial data on optimal therapy for CFRD. People with CFRD should be treated with insulin to attain individualized glycemic goals. See Section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information.

Additional resources for the clinical management of CFRD can be found in the position statement "Clinical Care Guidelines for Cystic Fibrosis-Related Diabetes" (136) and in the International Society for Pediatric

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and Adolescent Diabetes (ISPAD) 2022 clinical practice consensus guidelines (127).

## POSTTRANSPLANTATION DIABETES MELLITUS

***Recommendations***

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

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

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

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (137). New-onset diabetes after transplantation (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (138). Another term, posttransplantation diabetes mellitus (PTDM) (138,139), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset (140). The clinical importance of PTDM lies in its impact as a significant risk factor for cardiovascular disease and chronic kidney disease in solid-organ transplantation (137).

Hyperglycemia is very common during the early posttransplant period, with ∼90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (138,139,141,142). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (142,143). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression (138). Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, and obesity) and transplant-specific factors, such as use of immunosuppressant agents (144–146). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the individual is stable on maintenance immunosuppression (usually at least 45 days) and in the absence of acute infection (138,142–144,147).

The OGTT is recommended for the diagnosis of PTDM (1 year posttransplant) (138,139,148). However, screening people with FPG and/or A1C can identify high-risk individuals who require further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (144,149,150). Most studies have reported that transplant individuals with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (142,144,151). Insulin therapy is the agent of choice for the management of hyperglycemia and diabetes in the hospital setting and can be continued postdischarge. Noninsulin glucose-lowering therapies can also be used for long-term management. The choice of agent is usually made based on the side effect profile of the medication, possible interactions with the individual's immunosuppression plan, and potential cardiovascular and renal benefits in individuals with PTDM (144). See Section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information.

## MONOGENIC DIABETES SYNDROMES

***Recommendations***

**2.24a** Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have genetic testing for neonatal diabetes. **B**

**2.24b** Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY). **B**

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

Monogenic defects that cause β-cell dysfunction (e.g., neonatal diabetes and MODY) or insulin resistance syndromes (e.g., monogenic lipodystrophies) are present in a small fraction of people with diabetes (<5%) (152). **Table 2.7** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (153) and ISPAD 2022 clinical practice consensus guidelines (152).

### Diagnosis of Monogenic Diabetes

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

- Diabetes diagnosed within the first 6 months of life (152,154)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, and lacking other metabolic features, especially strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.6–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

### Neonatal Diabetes

Diabetes occurring under 6 months of age is termed neonatal diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (36,154–157). 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.

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**Table 2.7—Most common causes of monogenic diabetes**

| | Gene | Inheritance | Clinical features |
|---|---|---|---|
| **MODY** | *HNF1A* | AD | HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [>5 mmol/L]); low hs-CRP; sensitive to sulfonylureas |
| | *HNF4A* | AD | HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight (macrosomia) and transient neonatal hypoglycemia; sensitive to sulfonylureas |
| | *HNF1B* | AD | HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout |
| | *GCK* | AD | GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [<3 mmol/L]) |
| **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 (154) |
| | *FOXP3* | X-linked | Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring |

Adapted from Carmody et al. (153). 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.

The ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing (36). Correct diagnosis has critical implications, because 30–50% of people with $K_{ATP}$-related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, with insulin therapy being the preferred treatment strategy.

### Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 14 genes on different chromosomes identified to date (152). The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

Correct diagnosis of monogenic forms of diabetes is critical because people who have them may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment plans and delays in diagnosing other family members (152). 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 (155–162) (**Fig. 2.1**). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in people with monogenic diabetes has been reported. Individuals in whom monogenic diabetes is suspected should have genetic testing. Genetic screening (i.e., next-generation sequencing) is increasingly available and cost-effective (152). Consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis and to address comprehensive cardiovascular risk.

A diagnosis of one of the three most common forms of MODY, HNF1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective personalized therapy (i.e., no therapy for GCK-MODY and sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). See Section 9, "Pharmacologic Approaches to Glycemic

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Treatment," for further information. Additionally, diagnosis can lead to identification of other affected family members and can indicate potential extrapancreatic complications in affected individuals.

## GESTATIONAL DIABETES MELLITUS

***Recommendations***

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

**2.26a** Before 15 weeks of gestation, test individuals with risk factors (**Table 2.5**) **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.

**2.26b** Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus (GDM) diagnosis. **B**

**2.26c** Screen for early abnormal glucose metabolism with dysglycemia using FPG 110–125 mg/dL (6.1–6.9 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**

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

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

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

### Definition

For many years, gestational diabetes mellitus (GDM) was defined as any degree of glucose intolerance that was first recognized during pregnancy (86), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has limitations (163). First, the best evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy (164–166). Ideally, undiagnosed diabetes should be identified preconception in individuals with risk factors or in high-risk populations (167–172), as they are likely to benefit from preconception care. The preconception care of people with known preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission (173). If individuals are not screened prior to pregnancy, universal early screening at <15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (**Table 2.5**), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify these health disparities so that they can begin to address them (169–172). Diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in nonpregnant individuals (**Table 2.1**). Individuals found to have diabetes should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as a fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (41 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, and perinatal death), are at high risk of a later GDM diagnosis, and are more likely to need insulin treatment (174–176). An A1C threshold of 5.7% (39 mmol/L) has not been shown to be associated with adverse perinatal outcomes (177,178).

If early screenings for undiagnosed diabetes or early abnormal glucose metabolism were negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation and individuals not previously screened should be screened for GDM at the same time point (see Section 15, "Management of Diabetes in Pregnancy"). The GDM diagnostic criteria for the 75-g OGTT from the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) and the GDM screening and diagnostic criteria with the two-step approach were not derived from data in the first half of pregnancy and should not be used for early screening (179). Most randomized controlled trials of treatment of early abnormal glucose metabolism have been underpowered for outcomes. One randomized controlled trial performed at 17 centers administered early screening (mean 15.6 ± 2.5 weeks) for GDM with a 75-g OGTT. Individuals who met World Health Organization criteria for GDM were randomized to receive early treatment or a repeat OGTT at 24–28 weeks (with deferred treatment if indicated). The first primary outcome measure was an adverse neonatal composite outcome including birth <37 weeks, birth weight ≥4.5 kg, birth trauma, neonatal respiratory distress within 24 h of birth, phototherapy, stillbirth neonatal death, or shoulder dystocia. Early GDM treatment resulted in a modest improvement in the composite adverse neonatal outcome (24.9% early treatment vs. 30.5% control treatment, relative risk 0.82 [0.68–0.98]), although this was driven primarily by differences in rates of neonatal respiratory distress between groups that included neonates requiring ≥4 h of supplemental oxygen who may not have required a higher level of respiratory care. There was also a suggestion of more benefit (per prespecified subgroup analyses) among individuals who had the OGTT at <14 weeks and among those with OGTT glycemic values in higher ranges (180). Therefore, the benefits of treatment of early abnormal glucose metabolism remain uncertain. Nutrition counseling and periodic testing of glucose levels weekly to identify individuals with high glucose levels are suggested. Testing frequency may proceed to daily, and treatment may be intensified, if the FPG is predominantly >110 mg/dL (>6.1 mmol/L) prior to 18 weeks of gestation.

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Both the FPG and A1C are low-cost tests. An advantage of the A1C test is its convenience, as it can be added to the prenatal laboratories and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of increased red blood cell turnover and hemoglobinopathies (usually reads lower) and higher values with anemia and reduced red blood cell turnover (181). A1C is not reliable for screening for GDM or for preexisting diabetes at 15 weeks of gestation or later in part from the higher red blood cell turnover in pregnancy but also from the unknown diabetes status prior to pregnancy, which could help distinguish new-onset diabetes from preexisting diabetes.

GDM is often indicative of underlying β-cell dysfunction (182), which confers marked increased risk for later development of glucose intolerance and diabetes in the mother after delivery (183–185). As effective prevention interventions are available (186,187), individuals 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 (188).

**Table 2.8—Screening for and diagnosis of GDM**

**One-step strategy**

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

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

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

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

**Two-step strategy**

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

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

**Step 2:** The 100-g OGTT should be performed when the individual is fasting.

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

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

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (204). †ACOG notes that one elevated value can be used for diagnosis (204).

## Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (189), a large-scale multinational cohort study completed by more than 23,000 pregnant individuals, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

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

1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
2. The older "two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive based on the work of Carpenter-Coustan's interpretation of the older O'Sullivan and Mahan (190) criteria.

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

### *One-Step Strategy*

The IADPSG examined data from the HAPO study and defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in individuals at 24–28 weeks of gestation, wherein the cut points were those at which odds for adverse outcomes reached 1.75 times the estimated odds. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis (191). Many regional studies have seen a roughly one- to threefold increase in GDM cases using the IADPSG criteria (192). A study of pregnancy OGTTs with glucose levels blinded to caregivers found that 11 years after their pregnancies, individuals who would have been diagnosed with GDM by the one-step approach, as compared with those without GDM, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the group identified as having GDM by the one-step approach would benefit from the increased screening for diabetes and prediabetes after pregnancy (193). The ADA recommends the IADPSG diagnostic criteria to optimize gestational outcomes, because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

Expected benefits of using IADPSG criteria for offspring are inferred from intervention trials focusing on individuals with lower levels of hyperglycemia than those identified using older GDM diagnostic criteria. Those trials found modest benefits, including reduced rates of large-for-gestational-age births and preeclampsia (194,195). Of note, 80–90% of participants 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 the thresholds recommended by the IADPSG, and in one trial (195), 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

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different criteria have been published to date. However, a randomized trial of testing for GDM at 24–28 weeks of gestation by the one-step method using IADPSG criteria versus the two-step method by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications (196), though concerns were raised about sample size estimates and unanticipated suboptimal engagement with the screening and treatment protocol. For example, in the two-step group, 165 participants not counted as having GDM were treated for isolated elevated FPG >95 mg/dL (>5.3 mmol/L) (197).

The one-step method identifies long-term risks of maternal prediabetes and diabetes as well as offspring glucose intolerance and adiposity. Post hoc GDM in individuals diagnosed with this method in the HAPO cohort was associated with higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucose levels during the OGTT; and reduced insulin sensitivity and oral disposition index in their offspring at 10–14 years of age compared with offspring of mothers without GDM. Associations of mother's fasting, 1-h, and 2-h values on the 75-g OGTT were continuous with a comprehensive panel of offspring metabolic outcomes (198,199). HAPO Follow-up Study (HAPO FUS) data demonstrate that neonatal adiposity and fetal hyperinsulinemia (cord C-peptide), both higher across the continuum of maternal hyperglycemia, are mediators of childhood body fat (200).

Data are lacking on how the treatment of mother's hyperglycemia in pregnancy affects her offspring's risk for obesity, diabetes, and other metabolic disorders (201,202). Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of individuals with GDM diagnosed by the one-step strategy.

#### *Two-Step Strategy*

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (203). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended continuing a two-step approach to screening that used a 1-h 50-g glucose loading test (GLT) followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (204). A 2021 U.S. Preventive Services Task Force systematic review concluded that one-step versus two-step screening is associated with increased likelihood of GDM (11.5% vs. 4.9%) but without improved health outcomes (205). The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (206).

Importantly, the NIH panel noted the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of individuals with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and therefore is easier to accomplish for many individuals. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (207), 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 (204). If this approach is implemented, the incidence of GDM will likely increase markedly. ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT Carpenter-Coustan or National Diabetes Data Group (208,209). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan and Mahan (190), 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 (210) demonstrated that treatment was similarly beneficial in people meeting only the lower thresholds per Carpenter-Coustan (208) and in those meeting only the higher thresholds per National Diabetes Data Group (209). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds, as shown in step 2 in **Table 2.8**.

#### *Future Considerations*

Data exist to support each strategy, as demonstrated by conflicting recommendations by expert groups. A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method (211). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

The IADPSG criteria (one-step strategy) have been adopted internationally as the preferred approach. Data that compare population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (196,212–214). 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 (215,216). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit people with GDM, caregivers, and policymakers. Longer-term outcome studies are currently underway.

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