



## 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2022*

American Diabetes Association  
Professional Practice Committee\*

*Diabetes Care* 2022;45(Suppl. 1):S46–S59 | <https://doi.org/10.2337/dc22-S004>

The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (<https://doi.org/10.2337/dc22-SPPC>), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction (<https://doi.org/10.2337/dc22-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at [professional.diabetes.org/SOC](https://professional.diabetes.org/SOC).

### PATIENT-CENTERED COLLABORATIVE CARE

#### Recommendations

- 4.1 A patient-centered communication style that uses person-centered and strength-based language and active listening; elicits patient preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize patient health outcomes and health-related quality of life. **B**
- 4.2 People with diabetes can benefit from a coordinated multidisciplinary team that may include and is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. **E**

A successful medical evaluation depends on beneficial interactions between the patient and the care team. The Chronic Care Model (1–3) (see Section 1, “Improving Care and Promoting Health in Populations,” <https://doi.org/10.2337/dc22-S001>) is a patient-centered approach to care that requires a close working relationship between the patient and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interdisciplinary team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. Individuals with diabetes must assume an active role in their care. Based on patient

\*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at <https://doi.org/10.2337/dc22-SPPC>.

Suggested citation: American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45 (Suppl. 1):S46–S59

© 2021 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://diabetesjournals.org/journals/pages/license>.

preferences, the patient, family or support people, and health care team together formulate the management plan, which includes lifestyle management (see Section 5, “Facilitating Behavior Change and Well-being to Improve Health Outcomes,” <https://doi.org/10.2337/dc22-S005>).

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (Fig. 4.1). Treatment goals and plans should be created with patients based on their individual preferences, values, and goals. This individualized management plan should take into account the patient’s age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, current use of medications), comorbidities, disabilities, health priorities, other medical conditions, preferences for care, and life expectancy. Various strategies and

techniques should be used to support patients’ self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Provider communication with patients and families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–7). Thus, the goal of provider-patient communication is to establish a collaborative relationship and to assess and address self-management barriers without blaming patients for “noncompliance” or “nonadherence” when the outcomes of self-management are not optimal (8). The familiar terms “noncompliance” and “nonadherence” denote a passive, obedient role for a person with diabetes in “following doctor’s orders” that is at odds with the active role people with diabetes take in directing the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved

in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in self-management may help minimize patients’ resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the patient said, can help facilitate communication. Patients’ perceptions about their own ability, or self-efficacy, to self-manage diabetes constitute one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (9–11) and should be a target of ongoing assessment, patient education, and treatment planning.

Language has a strong impact on perceptions and behavior. The use of empowering language in diabetes care and education can help to inform and motivate people, yet language that shames and judges may undermine this effort. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (formerly

### DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



**Figure 4.1**—Decision cycle for patient-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (104).

called American Association of Diabetes Educators) joint consensus report, “The Use of Language in Diabetes Care and Education,” provides the authors’ expert opinion regarding the use of language by health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (12). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, non-judgmental, and based on facts, actions, or physiology/biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between patients and providers.
- Use language that is person centered (e.g., “person with diabetes” is preferred over “diabetic”).

## COMPREHENSIVE MEDICAL EVALUATION

### Recommendations

**4.3** A complete medical evaluation should be performed at the initial visit to:

- Confirm the diagnosis and classify diabetes. **A**
- Evaluate for diabetes complications and potential comorbid conditions. **A**
- Review previous treatment and risk factor control in patients with established diabetes. **A**
- Begin patient engagement in the formulation of a care management plan. **A**
- Develop a plan for continuing care. **A**

**4.4** A follow-up visit should include most components of the initial comprehensive medical evaluation (see **Table 4.1**). **A**

**4.5** Ongoing management should be guided by the assessment of overall health status, diabetes complications, cardiovascular risk, hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, and engagement of the patient throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the provider may need to prioritize the components of the medical evaluation given the available resources and time. The goal is to provide the health care team information so it can optimally support a patient. In addition to the medical history, physical examination, and laboratory tests, providers should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5, “Facilitating Behavior Change and Well-being to Improve Health Outcomes,” <https://doi.org/10.2337/dc22-S005>) and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered; a meta-analysis found that poor sleep quality, short sleep, and long sleep were associated with higher A1C in people with type 2 diabetes (13). Interval follow-up visits should occur at least every 3–6 months individualized to the patient, and then at least annually.

Lifestyle management and psychosocial care are the cornerstones of diabetes management. Patients should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of psychosocial/emotional health concerns if indicated. Patients should receive recommended preventive care services (e.g., immunizations, cancer screening, etc.); smoking cessation counseling; and ophthalmological, dental, and podiatric referrals, as needed.

The assessment of risk of acute and chronic diabetes complications and treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10, “Cardiovascular Disease and Risk Management,” <https://doi.org/10.2337/dc22-S010>), chronic kidney disease staging (see Section 11, “Chronic Kidney Disease and Risk Management,” <https://doi.org/10.2337/dc22-S011>), presence of retinopathy (see Section 12, “Retinopathy, Neuropathy, and Foot Care,” <https://doi.org/10.2337/dc22-S012>), and risk of treatment-associated hypoglycemia (**Table 4.3**) should be used to individualize targets for glycemia (see Section 6, “Glycemic Targets,” <https://doi.org/10.2337/dc22-S006>), blood pressure, and lipids and to select specific glucose-lowering medication (see Section 9, “Pharmacologic Approaches to Glycemic Treatment,” <https://doi.org/10.2337/dc22-S009>), antihypertension medication, and statin treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.4**). Clinicians should ensure that individuals with diabetes are appropriately screened for complications and comorbidities. Discussing and implementing an approach to glycemic control with the patient is a part, not the sole goal, of the patient encounter.

Additional referrals should be arranged as necessary (**Table 4.4**). Clinicians should ensure that individuals with diabetes are appropriately screened for complications and comorbidities. Discussing and implementing an approach to glycemic control with the patient is a part, not the sole goal, of the patient encounter.

## IMMUNIZATIONS

### Recommendation

**4.6** Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.5** for highly recommended vaccinations for adults with diabetes). **A**

The importance of routine vaccinations for people living with diabetes has been elevated by the coronavirus disease 2019 (COVID-19) pandemic. Preventing avoidable infections not only directly prevents morbidity but also reduces hospitalizations, which may additionally reduce risk of acquiring infections such as COVID-19. Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (14,15). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (see [www.cdc.gov/vaccines/](http://www.cdc.gov/vaccines/)). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.5** for selected vaccinations. The ACIP evidence review has evolved over time with the adoption of Grading of Recommendations Assessment, Development and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation frameworks

**Table 4.1 - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits**

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
<b>PAST MEDICAL AND FAMILY HISTORY</b>	<b>Diabetes history</b>			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment regimens and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	<b>Family history</b>			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	<b>Personal history of complications and common comorbidities</b>			
	▪ Common comorbidities (e.g., obesity, OSA, NAFLD)	✓		✓
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ Last dental visit	✓		✓
▪ Last dilated eye exam	✓		✓	
▪ Visits to specialists	✓	✓	✓	
<b>Interval history</b>				
▪ Changes in medical/family history since last visit		✓	✓	
<b>BEHAVIORAL FACTORS</b>	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
<b>MEDICATIONS AND VACCINATIONS</b>	▪ Current medication regimen	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
<b>TECHNOLOGY USE</b>	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use, connected pen and glucose data	✓	✓	✓
<b>SOCIAL LIFE ASSESSMENT</b>	<b>Social network</b>			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓

Continued on p. S50

**Table 4.1 (cont.)- Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits**

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
<b>PHYSICAL EXAMINATION</b>	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, and disordered eating	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
▪ Consider assessment for functional performance*	✓		✓	
<b>LABORATORY EVALUATION</b>	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides <sup>#</sup>	✓		✓ <sup>^</sup>
	• Liver function tests <sup>#</sup>	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate <sup>+</sup>	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes <sup>#</sup>	✓		✓
	• Vitamin B12 if on metformin	✓		✓
• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics <sup>+</sup>	✓		✓	

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA obstructive sleep apnea; PAD, peripheral arterial disease

\*At 65 years of age or older

+May be needed more frequently in patients with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see Table 11.1)

<sup>#</sup>May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications)

<sup>^</sup>In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent

\*\*Should be performed at every visit in patients with sensory loss, previous foot ulcers, or amputations

Downloaded from http://ada.literchair.com/care/article-pdf/45/Supplement\_1/S46/S37559/4c228004.pdf by guest on 27 June 2022

in 2018 (16). Here we discuss the particular importance of specific vaccines.

**Influenza**

Influenza is a common, preventable infectious disease associated with high mortality and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people

with diabetes has been found to significantly reduce influenza and diabetes-related hospital admissions (17). In patients with diabetes and cardiovascular disease, influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (18). Given the benefits of the annual influenza vaccination, it is recommended for all individuals ≥6 months of age who do

not have a contraindication. Influenza vaccination is critically important in the next year as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses will both be active in the U.S. during the 2021–2022 season (19). The live attenuated influenza vaccine, which is delivered by nasal spray, is an option for patients who are age 2 years through age 49 years and who are

**Table 4.2—Assessment and treatment plan\***

## Assessing risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (see **Table 4.3**)
- Assessment for retinopathy
- Assessment for neuropathy

## Goal setting

- Set A1C/blood glucose/time in range target
- If hypertension is present, establish blood pressure target
- Diabetes self-management goals

## Therapeutic treatment plans

- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and renal disease risk factors
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. \*Assessment and treatment planning are essential components of initial and all follow-up visits.

not pregnant, but patients with chronic conditions such as diabetes are cautioned against taking the live attenuated influenza vaccine and are instead recommended to receive the inactive or recombinant influenza vaccination. For individuals  $\geq 65$  years of age, there may be additional benefit from the high-dose quadrivalent inactivated influenza vaccine (19).

**Pneumococcal Pneumonia**

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, with a mortality rate as high as 50% (20). There are two vaccination types, the 23-valent pneumococcal polysaccharide vaccine (PPSV23)

and the 13-valent pneumococcal conjugate vaccine (PCV13), with distinct schedules for children and adults.

All children are recommended to receive a four-dose series of PCV13 by 15 months of age. For children with diabetes who have incomplete series by ages 2–5 years, the CDC recommends a catch-up schedule to ensure that these children have four doses. Children with diabetes between 6–18 years of age are also advised to receive one dose of PPSV23, preferably after receipt of PCV13.

For adults with diabetes, one dose of PPSV23 is recommended between the ages of 19 and 64 years and another dose at  $\geq 65$  years of age. The PCV13 is no longer routinely recommended for patients over 65 years of age because of the declining rates of pneumonia attributable to these strains (21). Older patients should have a shared decision-making discussion with their provider to determine individualized risks and benefits. PCV13 is recommended for patients with immunocompromising conditions such as asplenia, advanced kidney disease, cochlear implants, or cerebrospinal fluid leaks (22). Some older patients residing in assisted living facilities may also consider PCV13. If the PCV13 is to be administered, it should be given prior to the next dose of PPSV23.

**Table 4.3—Assessment of hypoglycemia risk**

## Factors that increase risk of treatment-associated hypoglycemia

- Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
- Impaired kidney or hepatic function
- Longer duration of diabetes
- Frailty and older age
- Cognitive impairment
- Impaired counterregulatory response, hypoglycemia unawareness
- Physical or intellectual disability that may impair behavioral response to hypoglycemia
- Alcohol use
- Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective  $\beta$ -blockers)
- History of severe hypoglycemic event

In addition to individual risk factors, consider use of comprehensive risk prediction models (105).

See references 106–110.

**Table 4.4—Referrals for initial care management**

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian nutritionist for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Mental health professional, if indicated
- Audiology, if indicated
- Social worker/community resources, if indicated

**Hepatitis B**

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis B. This may be due to contact with infected blood or through improper equipment use (glucose monitoring devices or infected needles). Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes aged  $< 60$  years. For adults aged  $\geq 60$  years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the patient's likelihood of acquiring hepatitis B infection.

**COVID-19**

As of August 2021, the COVID-19 vaccines are recommended for all adults and some children, including people with diabetes, under full approval of the U.S. Food and Drug Administration. The three options in the U.S. are the mRNA vaccines from Pfizer-BioNTech and

**Table 4.5—Highly recommended immunizations for adult patients with diabetes (Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention)**

Vaccination	Age-group recommendations	Frequency	GRADE evidence type*	Reference
Hepatitis B	<60 years of age; ≥60 years of age discuss with health care provider	Two- or three-dose series	2	Centers for Disease Control and Prevention, Use of Hepatitis B Vaccination for Adults With Diabetes Mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (111)
Human papilloma virus (HPV)	≤26 years of age; 27–45 years of age may also be vaccinated against HPV after a discussion with health care provider	Three doses over 6 months	2 for females, 3 for males	Meites et al., Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices (112)
Influenza	All patients; advised not to receive live attenuated influenza vaccine	Annual	–	Demicheli et al., Vaccines for Preventing Influenza in the Elderly (113)
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose	2	Centers for Disease Control and Prevention, Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) (114)
	≥65 years of age, obtain second dose of Pneumovax, at least 5 years from prior Pneumovax vaccine	One dose; if PCV13 has been given, then give PPSV23 ≥1 year after PCV13 and ≥5 years after any PPSV23 at age <65 years	2	Falkenhorst et al., Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) Against Pneumococcal Disease in the Elderly: Systematic Review and Meta-analysis (115)
Pneumonia (PCV13 [Prenar])	Adults ≥19 of age, with an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak	One dose	3	Matanock et al., Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Updated Recommendations of the Advisory Committee on Immunization Practices (21)
	19–64 years of age, immunocompetent, no recommendation	None		
	≥65 years of age, immunocompetent, have shared decision-making discussion with health care provider	One dose		
Tetanus, diphtheria, pertussis (TDAP)	All adults; pregnant women should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers et al., Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2019 (116)

Continued on p. S53

Table 4.5—Continued

Vaccination	Age-group recommendations	Frequency	GRADE evidence type*	Reference
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling et al., Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines (117)

GRADE, Grading of Recommendations Assessment, Development and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. \*Evidence type: 1 = randomized controlled trials (RCTs), or overwhelming evidence from observational studies; 2 = RCTs with important limitations, or exceptionally strong evidence from observational studies; 3 = observational studies, or RCTs with notable limitations; and 4 = clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations. For a comprehensive list, refer to the Centers for Disease Control and Prevention at [www.cdc.gov/vaccines/](http://www.cdc.gov/vaccines/).

Moderna and the recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine from Janssen. Pfizer-BioNTech vaccine is recommended for people aged 12 years and older, with a grade 1 evidence rating for the prevention of symptomatic COVID-19 (23,24). It is given as a two-shot series 21 days apart. Moderna vaccine is recommended for people aged 18 years and older, with a grade 1 evidence rating for prevention of symptomatic COVID-19 (23). It is given as a two-shot series 28 days apart. Janssen vaccine is also recommended for people aged 18 years and older, with a grade 2 evidence rating (25). Unlike the mRNA vaccines, only one shot is required. Evidence regarding the efficacy of mixing vaccines is still emerging. Booster vaccine recommendations are also evolving, with the CDC just recently recommending the Pfizer-BioNTech booster for older adults and those with underlying conditions such as diabetes. The COVID-19 vaccine will likely become a routine part of the annual preventive schedule for people with diabetes.

## ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and their patients need to be aware of common comorbidities that affect people with diabetes and that may complicate management (26–30). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section discusses many of the common comorbidities observed in patients with diabetes but is not necessarily inclusive of all the conditions that have been reported.

## Autoimmune Diseases

### Recommendations

- 4.7** Patients with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter. **B**
- 4.8** Adult patients with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, or laboratory manifestations suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (31). Other associated conditions include autoimmune hepatitis, primary adrenal insufficiency (Addison disease), collagen vascular diseases, and myasthenia gravis (32–35). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (36). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all patients with type 1 diabetes. Screening for celiac disease should be considered in adult patients with suggestive symptoms (e.g., diarrhea, malabsorption, abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, iron deficiency anemia) (37,38). Measurement of vitamin B12 levels should be considered for patients with type 1 diabetes and peripheral neuropathy or unexplained anemia.

## Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (39). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (40), such as underlying disease physiology or diabetes treatments, although evidence for these links is scarce. Patients with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus, negative family history) in a middle-aged or older patient may precede the diagnosis of pancreatic adenocarcinoma (41). However, in the absence of other symptoms (e.g., weight loss, abdominal pain), routine screening of all such patients is not currently recommended.

## Cognitive Impairment/Dementia

### Recommendation

- 4.9** In the presence of cognitive impairment, diabetes treatment regimens should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (42,43). A recent meta-analysis of prospective observational studies in people with diabetes showed 73% increased risk of all types of dementia, 56% increased



risk of Alzheimer dementia, and 127% increased risk of vascular dementia compared with individuals without diabetes (44). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (45). See Section 13, "Older Adults" (<https://doi.org/10.2337/dc22-S013>), for a more detailed discussion regarding screening for cognitive impairment.

#### Hyperglycemia

In those with type 2 diabetes, the degree and duration of hyperglycemia are related to dementia. More rapid cognitive decline is associated with both increased A1C and longer duration of diabetes (44). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that each 1% higher A1C level was associated with lower cognitive function in individuals with type 2 diabetes (46). However, the ACCORD study found no difference in cognitive outcomes in participants randomly assigned to intensive and standard glycemic control, supporting the recommendation that intensive glucose control should not be advised for the improvement of cognitive function in individuals with type 2 diabetes (47).

#### Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. In a long-term study of older patients with type 2 diabetes, individuals with one or more recorded episodes of severe hypoglycemia had a stepwise increase in risk of dementia (48). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (49). Tailoring glycemic therapy may help to prevent hypoglycemia in individuals with cognitive dysfunction. See Section 13, "Older Adults" (<https://doi.org/10.2337/dc22-S013>), for more detailed discussion of hypoglycemia

in older patients with type 1 and type 2 diabetes.

#### Nutrition

In one study, adherence to the Mediterranean diet correlated with improved cognitive function (50). However, a recent Cochrane review found insufficient evidence to recommend any specific dietary change for the prevention or treatment of cognitive dysfunction (51).

#### Statins

A systematic review has reported that data do not support an adverse effect of statins on cognition (52). The U.S. Food and Drug Administration postmarketing surveillance databases have also revealed a low reporting rate for cognitive-related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (52). Therefore, fear of cognitive decline should not be a barrier to statin use in individuals with diabetes and a high risk for cardiovascular disease.

#### Nonalcoholic Fatty Liver Disease

##### Recommendation

**4.10** Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

Diabetes is associated with the development of nonalcoholic fatty liver disease (NAFLD), including its more severe manifestations of nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma (53). Elevations of hepatic transaminase concentrations are associated with higher BMI, waist circumference, and triglyceride levels and lower HDL cholesterol levels. Noninvasive tests, such as elastography or fibrosis biomarkers, may be used to assess risk of fibrosis, but referral to a liver specialist and liver biopsy may be required for definitive diagnosis (54). Interventions that improve metabolic abnormalities in patients with diabetes (weight loss, glycemic control, and treatment with specific drugs for hyperglycemia or dyslipidemia)

are also beneficial for fatty liver disease (55,56). Pioglitazone, vitamin E treatment, liraglutide, and semaglutide treatment of biopsy-proven NASH have each been shown to improve liver histology, but effects on longer-term clinical outcomes are not known (57–59). Treatment with other glucagon-like peptide 1 receptor agonists and with sodium–glucose cotransporter 2 inhibitors has shown promise in preliminary studies, although benefits may be mediated, at least in part, by weight loss (59–61).

The American Gastroenterological Association convened an international conference, including representatives of the ADA, to review and discuss published literature on burden, screening, risk stratification, diagnosis, and management of individuals with NAFLD, including NASH (62). Please see the special report "Preparing for the NASH Epidemic: A Call to Action" for full details (62). Significant gaps were identified, including gaps in knowledge in who to screen and how to diagnose and treat patients at high risk for NASH. In patients with suspected NAFLD, diagnosis consists of evaluating patients for alternative or coexisting causes of liver disease through history and laboratory testing. In patients with NAFLD/NASH, risk stratification with non-invasive fibrosis scores was suggested. **Table 4.6**, reproduced from the special report, summarizes the management recommendations for patients with NAFLD and NASH, and **Table 4.7** presents the summary of published NAFLD guidelines included in the report (62). Further research and interdisciplinary consensus are required to fully define screening, referral, and diagnostic pathways.

#### Hepatitis C Infection

Infection with hepatitis C virus (HCV) is associated with a higher prevalence of type 2 diabetes, which is present in up to one-third of individuals with chronic HCV infection. HCV may impair glucose metabolism by several mechanisms, including directly via viral proteins and indirectly by altering proinflammatory cytokine levels (63). The use of newer direct-acting antiviral drugs produces a sustained virological response (cure) in nearly all cases and has been reported to improve glucose metabolism in individuals with diabetes (64). A meta-analysis of mostly observational studies

found a mean reduction in A1C levels of 0.45% (95% CI −0.60 to −0.30) and reduced requirement for glucose-lowering medication use following successful eradication of HCV infection (65).

**Pancreatitis**

Diabetes is linked to diseases of the exocrine pancreas such as pancreatitis, which may disrupt the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction. Up to half of patients with diabetes may have some degree of impaired exocrine pancreas function (66). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (67).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of patients after an episode of acute pancreatitis (68); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (69). Studies of patients treated with incretin-based therapies for diabetes have also reported that pancreatitis may occur more frequently with these medications, but results have been mixed and causality has not been established (70–72).

Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Approximately one-third of patients undergoing total pancreatectomy with islet autotransplantation are insulin free 1 year postoperatively, and observational studies from different centers have demonstrated islet graft function up to a

decade after the surgery in some patients (73–77). Both patient and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet autotransplantation.

**Fractures**

Age-specific hip fracture risk is significantly increased in both people with type 1 diabetes (relative risk 6.3) and those with type 2 diabetes (relative risk 1.7) in both sexes (78). Type 1 diabetes is associated with osteoporosis, but in type 2 diabetes, an increased risk of hip fracture is seen despite higher bone mineral density (BMD) (79). In three large observational studies of older adults, femoral neck BMD T-score and the World Health Organization Fracture Risk Assessment Tool (FRAX) score were associated with hip and nonspine fractures. Fracture risk was higher in participants with diabetes compared with those without diabetes for a given T-score and age or for a given FRAX score (80). Providers should assess fracture history and risk factors in older patients with diabetes and recommend measurement of BMD if appropriate for the patient’s age and sex. Fracture prevention strategies for people with diabetes are the same as for the general population and may include vitamin D supplementation. For patients with type 2 diabetes with fracture risk factors, thiazolidinediones (81) and sodium–glucose cotransporter 2 inhibitors (82) should be used with caution.

**Sensory Impairment**

Hearing impairment, both in high-frequency and low- to midfrequency ranges, is more common in people with diabetes than in those without, with stronger associations found in studies of younger people (83). Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress to cochlear microangiopathy and auditory neuropathy (84). In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes compared with those without, after adjusting for age and other risk factors for hearing impairment (85). Low HDL cholesterol, coronary heart disease, peripheral neuropathy, and general poor health have been reported as risk factors for hearing impairment for people with diabetes, but an association of hearing loss with blood glucose levels has not been consistently observed (86). In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, time-weighted mean A1C was associated with increased risk of hearing impairment when tested after long-term (>20 years) follow-up (87). Impairment in smell, but not taste, has also been reported in individuals with diabetes (88).

**Low Testosterone in Men**

**Recommendation**

**4.11** In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity, or

**Table 4.6—Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis**

Variable	Lifestyle intervention <sup>a</sup>	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFLD	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists <sup>b</sup>	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize <sup>c</sup>	Yes

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. <sup>a</sup>All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended. <sup>b</sup>Among glucagon-like peptide 1 (GLP-1) receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis. <sup>c</sup>Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution. Adapted from “Preparing for the NASH Epidemic: A Call to Action” (62).

**Table 4.7—Summary of published nonalcoholic fatty liver disease guidelines**

Organization	Year	First-line diagnosis test	When to refer to hepatologist	Noninvasive tests
American Association for the Study of Liver Diseases (AASLD)	2018	Not clear in the guideline Routine screening for NAFLD in high-risk groups is not recommended	Not clear in the guideline	Diagnosis for NASH: liver biopsy Assessment for fibrosis: NFS or FIB-4
American Gastroenterological Association (AGA)	2012	Routine screening for NAFLD is not recommended	Not clear in the guideline	Metabolic syndrome can be used to target patients for liver biopsy
European Association for the Study of the Liver (EASL)	2016	Ultrasound + liver enzymes for patients with risk factors	Refer patients with abnormal liver enzymes or medium-/high-risk fibrosis markers to specialist	Diagnosis for NASH: liver biopsy Assessment for fibrosis: NFS or FIB-4
World Gastroenterology Organization (WGO)	2012	Ultrasound + liver enzymes for patients with risk factors	Not clear in the guideline	Diagnosis for NASH: liver biopsy
National Institute for Health Care and Excellence (NICE)	2016	Ultrasound + liver enzymes for patients with risk factors But routine liver function blood tests are not sensitive, and ultrasound is not cost-effective	Refer adults with advanced liver fibrosis to a hepatologist Refer children with suspected NAFLD to a pediatric specialist in hepatology	Assessment for advanced fibrosis: enhanced liver fibrosis (every 2–3 years)

FIB-4, Fibrosis-4 Index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score. Adapted from "Preparing for the NASH Epidemic: A Call to Action" (62).

erectile dysfunction, consider screening with a morning serum testosterone level. **B**

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (89,90). Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density (91). In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay (92). In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, sex hormone binding globulin, and albumin concentrations (92). Please see the Endocrine Society clinical practice guideline for detailed recommendations (92). Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to further evaluate the patient. Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery

plaque volume, with no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in hypogonadal men (92).

#### Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (93). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (94,95). In participants with obesity enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (96). Patients with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, witnessed apnea) should be considered for screening (97). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure control. The evidence for a treatment effect on glycemic control is mixed (98).

#### Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in patients with diabetes than in those without and has

been associated with higher A1C levels (99–101). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (30,102). In a randomized clinical trial, intensive periodontal treatment was associated with better glycemic control (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and reduction in inflammatory markers after 12 months of follow-up (103).

#### References

1. Stelfox M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013;10:E26
2. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health Aff (Millwood)* 2009;28:75–85
3. Gabbay RA, Bailit MH, Mauger DT, Wagner EH, Siminerio L. Multipayer patient-centered medical home implementation guided by the chronic care model. *Jt Comm J Qual Patient Saf* 2011;37:265–273
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
5. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J,

- et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
6. Lachin JM, Genuth S, Nathan DM, Zinman B; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial—revisited. *Diabetes* 2008;57:995–1001
7. White NH, Cleary PA, Dahms W, Goldstein D, Malone J; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001;139:804–812
8. Anderson RM, Funnell MM. Compliance and adherence are dysfunctional concepts in diabetes care. *Diabetes Educ* 2000;26:597–604
9. Sarkar U, Fisher L, Schillinger D. Is self-efficacy associated with diabetes self-management across race/ethnicity and health literacy? *Diabetes Care* 2006;29:823–829
10. King DK, Glasgow RE, Toobert DJ, et al. Self-efficacy, problem solving, and social-environmental support are associated with diabetes self-management behaviors. *Diabetes Care* 2010;33:751–753
11. Nouwen A, Urquhart Law G, Hussain S, McGovern S, Napier H. Comparison of the role of self-efficacy and illness representations in relation to dietary self-care and diabetes distress in adolescents with type 1 diabetes. *Psychol Health* 2009;24:1071–1084
12. Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. *Diabetes Care* 2017;40:1790–1799
13. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev* 2017;31:91–101
14. Robinson CL, Bernstein H, Poehling K, Romero JR, Szilagyi P. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger – United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:130–132
15. Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older – United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:133–135
16. Lee G, Carr W; ACIP Evidence-Based Recommendations Work Group. Updated framework for development of evidence-based recommendations by the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2018;67:1271–1272
17. Goeijenbier M, van Sloten TT, Slobbe L, et al. Benefits of flu vaccination for persons with diabetes mellitus: a review. *Vaccine* 2017;35:5095–5101
18. Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;10:e019636
19. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices – United States, 2020–21 influenza season. *MMWR Recomm Rep* 2020;69:1–24
20. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 2000;23:95–108
21. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Piliushvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged  $\geq 65$  years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2019;68:1069–1075
22. Ahmed SS, Pondo T, Xing W, et al. Early impact of 13-valent pneumococcal conjugate vaccine use on invasive pneumococcal disease among adults with and without underlying medical conditions—United States. *Clin Infect Dis* 2020;70:2484–2492
23. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine – United States, December 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1922–1924
24. Wallace M, Woodworth KR, Gargano JW, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12–15 years – United States, May 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:749–752
25. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Janssen COVID-19 vaccine – United States, February 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:329–332
26. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. *Diabetes Care* 2006;29:2415–2419
27. Grant RW, Ashburner JM, Hong CS, Chang Y, Barry MJ, Atlas SJ. Defining patient complexity from the primary care physician's perspective: a cohort study [published correction appears in *Ann Intern Med* 2012;157:152]. *Ann Intern Med* 2011;155:797–804
28. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition—multimorbidity. *JAMA* 2012;307:2493–2494
29. Sudore RL, Karter AJ, Huang ES, et al. Symptom burden of adults with type 2 diabetes across the disease course: Diabetes & Aging Study. *J Gen Intern Med* 2012;27:1674–1681
30. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Periodontol* 2013;84 (Suppl.):S135–S152
31. Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. *Eur J Endocrinol* 2019;180:135–144
32. De Block CE, De Leeuw IH, Van Gaal LF. High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. *J Clin Endocrinol Metab* 1999;84:4062–4067
33. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011;34:1211–1213
34. Hughes JW, Riddlesworth TD; T1D Exchange Clinic Network. Autoimmune diseases in children and adults with type 1 diabetes from the T1D Exchange Clinic Registry. *J Clin Endocrinol Metab* 2016;101:4931–4937
35. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. *Autoimmun Rev* 2016;15:644–648
36. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004;350:2068–2079
37. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656–676; quiz 677
38. Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease—changing utility of serology and histologic measures: expert review. *Gastroenterology* 2019;156:885–889
39. Suh S, Kim K-W. Diabetes and cancer: is diabetes causally related to cancer? *Diabetes Metab J* 2011;35:193–198
40. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 2010;60:207–221
41. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas* 2013;42:198–201
42. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia* 2005;48:2460–2469
43. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64–74
44. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J Diabetes Investig* 2013;4:640–650
45. Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. *Neurology* 2011;77:1126–1134
46. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al.; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. *Diabetes Care* 2009;32:221–226
47. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND):

- a randomised open-label substudy. *Lancet Neurol* 2011;10:969–977
48. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
49. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care* 2012;35:787–793
50. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol* 2009;66:216–225
51. Ooi CP, Loke SC, Yassin Z, Hamid T-A. Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment. *Cochrane Database Syst Rev* 2011;4:CD007220
52. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688–697
53. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004;126:460–468
54. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–357
55. American Gastroenterological Association. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. *Gastroenterology* 2002;123:1702–1704
56. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305–315
57. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297–2307
58. Sanyal AJ, Chalasani N, Kowdley KV, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362:1675–1685
59. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679–690
60. Shimizu M, Suzuki K, Kato K, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetes Obes Metab* 2019;21:285–292
61. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia* 2020;63:2434–2445
62. Kanwal F, Shubrook JH, Younossi Z, et al. Preparing for the NASH epidemic: a call to action. *Diabetes Care* 2021;44:2162–2172
63. Lecube A, Hernández C, Genescà J, Simó R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. *Diabetes Care* 2006;29:1096–1101
64. Hum J, Jou JH, Green PK, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. *Diabetes Care* 2017;40:1173–1180
65. Carnovale C, Pozzi M, Dassano A, et al. The impact of a successful treatment of hepatitis C virus on glyco-metabolic control in diabetic patients: a systematic review and meta-analysis. *Acta Diabetol* 2019;56:341–354
66. Piciocchi M, Capurso G, Archibugi L, Delle Fave MM, Capasso M, Delle Fave G. Exocrine pancreatic insufficiency in diabetic patients: prevalence, mechanisms, and treatment. *Int J Endocrinol* 2015;2015:595649
67. Lee Y-K, Huang M-Y, Hsu C-Y, Su Y-C. Bidirectional relationship between diabetes and acute pancreatitis: a population-based cohort study in Taiwan. *Medicine (Baltimore)* 2016;95:e2448
68. Das SLM, Singh PP, Phillips ARJ, Murphy R, Windsor JA, Petrov MS. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. *Gut* 2014;63:818–831
69. Petrov MS. Diabetes of the exocrine pancreas: American Diabetes Association-compliant lexicon. *Pancreatol* 2017;17:523–526
70. Thomsen RW, Pedersen L, Møller N, Kahlert J, Beck-Nielsen H, Sørensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. *Diabetes Care* 2015;38:1089–1098
71. Tkáč I, Raz I. Combined analysis of three large interventional trials with gliptins indicates increased incidence of acute pancreatitis in patients with type 2 diabetes. *Diabetes Care* 2017;40:284–286
72. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med* 2014;370:794–797
73. Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. *Ann Surg* 2015;261:21–29
74. Sutherland DER, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 2012;214:409–424; discussion 424–426
75. Quartuccio M, Hall E, Singh V, et al. Glycemic predictors of insulin independence after total pancreatectomy with islet autotransplantation. *J Clin Endocrinol Metab* 2017;102:801–809
76. Webb MA, Illouz SC, Pollard CA, et al. Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. *Pancreas* 2008;37:282–287
77. Wu Q, Zhang M, Qin Y, et al. Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients. *Endocr J* 2015;62:227–234
78. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 2007;166:495–505
79. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int* 2007;18:427–444
80. Schwartz AV, Vittinghoff E, Bauer DC, et al.; Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA* 2011;305:2184–2192
81. Kahn SE, Zinman B, Lachin JM, et al.; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2008;31:845–851
82. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. *Lancet Diabetes Endocrinol* 2015;3:8–10
83. Baiduc RR, Helzner EP. Epidemiology of diabetes and hearing loss. *Semin Hear* 2019;40:281–291
84. Helzner EP, Contrera KJ. Type 2 diabetes and hearing impairment. *Curr Diab Rep* 2016;16:3
85. Bainbridge KE, Hoffman HJ, Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. *Ann Intern Med* 2008;149:1–10
86. Bainbridge KE, Hoffman HJ, Cowie CC. Risk factors for hearing impairment among U.S. adults with diabetes: National Health and Nutrition Examination Survey 1999–2004. *Diabetes Care* 2011;34:1540–1545
87. Schade DS, Lorenzi GM, Braffett BH, et al.; DCCT/EDIC Research Group. Hearing impairment and type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *Diabetes Care* 2018;41:2495–2501
88. Rasmussen VF, Vestergaard ET, Hejlesen O, Andersson CUN, Cichosz SL. Prevalence of taste and smell impairment in adults with diabetes: a cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES). *Prim Care Diabetes* 2018;12:453–459
89. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010;33:1186–1192
90. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. *J Clin Endocrinol Metab* 2011;96:2341–2353
91. Bhasin S, Cunningham GR, Hayes FJ, et al.; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536–2559
92. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018;103:1715–1744
93. Li C, Ford ES, Zhao G, Croft JB, Balluz LS, Mokdad AH. Prevalence of self-reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005–2006. *Prev Med* 2010;51:18–23
94. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006;61:945–950

95. Resnick HE, Redline S, Shahar E, et al.; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care* 2003;26:702–709
96. Foster GD, Sanders MH, Millman R, et al.; Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* 2009;32:1017–1019
97. Bibbins-Domingo K, Grossman DC, Curry SJ, et al.; US Preventive Services Task Force. Screening for obstructive sleep apnea in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2017;317:407–414
98. Shaw JE, Punjabi NM, Wilding JP, Alberti KGMM; International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008;81:2–12
99. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications* 2006;20:59–68
100. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. *Br Dent J* 2014;217:433–437
101. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US adults: National Health and Nutrition Examination Survey 2009–2014. *J Am Dent Assoc* 2018;149:576–588.e6
102. Simpson TC, Weldon JC, Worthington HV, et al. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst Rev* 2015;11:CD004714
103. D’Aiuto F, Gkraniias N, Bhowruth D, et al.; TASTE Group. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *Lancet Diabetes Endocrinol* 2018;6:954–965
104. Davies MJ, D’Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701
105. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. *JAMA Intern Med* 2017;177:1461–1470
106. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med* 2014;174:1116–1124
107. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 1997;157:1681–1686
108. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, Sinclair AJ. Hypoglycemia in older people – a less well recognized risk factor for frailty. *Aging Dis* 2015;6:156–167
109. Yun J-S, Ko S-H, Ko S-H, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. *Diabetes Care* 2013;36:1283–1289
110. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. *Drugs Aging* 2004;21:511–530
111. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60:1709–1711
112. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2019;68:698–702
113. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2018;2:CD004876
114. Centers for Disease Control and Prevention. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR* 2010;59:1102–1106
115. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. *PLoS ONE* 2017;12:e0169368
116. Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices–United States, 2019. *MMWR* 2020;69:77–83
117. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR* 2018;67:103–108