Adult-Onset Type 1 Diabetes: Current Understanding and Challenges

Diabetes Care 2021;44:2449–2456 | https://doi.org/10.2337/dc21-0770

R. David Leslie,[1] Carmella Evans-Molina,[2,3] Jacquelyn Freund-Brown,[4] Raffaella Buzzetti,[5] Dana Dabelea,[6] Kathleen M. Gillespie,[7] Robin Goland,[8] Angus G. Jones,[9] Mark Kacher,[4] Lawrence S. Phillips,[10] Olov Rolandsson,[11] Jana L. Wardian,[12] and Jessica L. Dunne[4]

Recent epidemiological data have shown that more than half of all new cases of type 1 diabetes occur in adults. Key genetic, immune, and metabolic differences exist between adult- and childhood-onset type 1 diabetes, many of which are not well understood. A substantial risk of misclassification of diabetes type can result. Notably, some adults with type 1 diabetes may not require insulin at diagnosis, their clinical disease can masquerade as type 2 diabetes, and the consequent misclassification may result in inappropriate treatment. In response to this important issue, JDRF convened a workshop of international experts in November 2019. Here, we summarize the current understanding and unanswered questions in the field based on those discussions, highlighting epidemiology and immunogenetic and metabolic characteristics of adult-onset type 1 diabetes as well as disease-associated comorbidities and psychosocial challenges. In adult-onset, as compared with childhood-onset, type 1 diabetes, HLA-associated risk is lower, with more protective genotypes and lower genetic risk scores; multiple diabetes-associated autoantibodies are decreased, though GADA remains dominant. Before diagnosis, those with autoantibodies progress more slowly, and at diagnosis, serum C-peptide is higher in adults than children, with ketoacidosis being less frequent. Tools to distinguish types of diabetes are discussed, including body phenotype, clinical course, family history, autoantibodies, comorbidities, and C-peptide. By providing this perspective, we aim to improve the management of adults presenting with type 1 diabetes.

Clinically, it has been relatively easy to distinguish the acute, potentially lethal, childhood-onset diabetes from the less aggressive condition that affects adults. However, experience has taught us that not all children with diabetes are insulin dependent and not all adults are non–insulin dependent. Immune, genetic, and metabolic analysis of these two, apparently distinct, forms of diabetes revealed inconsistencies, such that insulin-dependent and immune-mediated diabetes was redefined as type 1 diabetes, while most other forms were relabeled as type 2 diabetes. Recent data suggest a further shift in our thinking, with the recognition that more than half of all new cases of type 1 diabetes occur in adults. However, many adults may not require insulin at diagnosis of type 1 diabetes and have a more gradual onset of hyperglycemia, often leading to misclassification and inappropriate care. Indeed, misdiagnosis occurs in nearly 40% of adults with new type 1 diabetes, with the risk of error increasing with age (1,2). To consider this important issue, JDRF convened a workshop of international experts in November 2019 in New York, NY. In this Perspective, based on that workshop, we outline the evidence for

[1]*Centre for Immunobiology, Blizard Institute, Queen Mary University of London, London, U.K.*
[2]*Departments of Pediatrics and Medicine and Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN*
[3]*Richard L. Roudebush VA Medical Center, Indianapolis, IN*
[4]*JDRF, New York, NY*
[5]*Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy*
[6]*Lifecourse Epidemiology of Adiposity & Diabetes Center, Colorado School of Public Health, and Departments of Epidemiology and Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO*
[7]*Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, U.K.*
[8]*Naomi Berrie Diabetes Center, Columbia University, New York, NY*
[9]*Institute of Biomedical and Clinical Science, University of Exeter, Exeter, U.K.*
[10]*Atlanta VA Medical Center and Division of Endocrinology, Metabolism, and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA*
[11]*Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden*
[12]*College of Medicine, University of Nebraska Medical Center, Omaha, NE*

Corresponding author: Carmella Evans-Molina, cevansmo@iu.edu, or R. David Leslie, r.d.g.leslie@qmul.ac.uk

Received 7 April 2021 and accepted 12 August 2021

a new viewpoint, suggesting future directions of research and ways to alter disease management to help adults living with type 1 diabetes.

UNDERSTANDING ADULT-ONSET TYPE 1 DIABETES

Incidence of Type 1 Diabetes Among Adults Worldwide

Adult-onset type 1 diabetes is more common than childhood-onset type 1 diabetes, as shown from epidemiological data from both high-risk areas such as Northern Europe and low-risk areas such as China (3–8). In southeastern Sweden, the disease incidence among individuals aged 0–19 years is similar to that among individuals 40–100 years of age (37.8 per 100,000 persons per year and 34.0/100,000/year, respectively) (3). Given that the comparable incidence spans only two decades in children, it follows that adult-onset type 1 diabetes is more prevalent. Similarly, analysis of U.S. data from commercially insured individuals demonstrated an overall lower incidence in individuals 20–64 years of age (18.6/100,000/year) than in youth aged 0–19 years (34.3/100,000/year), but the total number of new cases in adults over a 14-year period was 19,174 compared with 13,302 in youth (4). Despite the incidence of childhood-onset type 1 diabetes in China being among the lowest in the world, prevalence data show similar trends across the life span. From 2010–2013, the incidence was 1.93/100,000 among individuals aged 0–14 years and 1.28/100,000 among those 15–29 years of age versus 0.69/100,000 among older adults (5). In aggregate, adults comprised 65.3% of all clinically defined newly diagnosed type 1 diabetes cases in China, which is similar to estimates using genetically stratified data from the population-based UK Biobank using a childhood-onset polygenic genetic risk score (GRS) (6). It is important to note that the proportion would likely be higher if autoimmune cases not requiring insulin initially were classified as type 1 diabetes. For example, in a clinic-based European study, the proportion of adults with diabetes not initially requiring insulin yet with type 1 diabetes–associated autoantibodies was even higher than those started on insulin at diagnosis with a defined type 1 diabetes diagnosis (9). Moreover, in an adult population-based study in China, the fraction (8.6%) with diabetes not requiring insulin yet with type 1 diabetes–associated autoantibodies was similar to that in Europe, implying that there could be over 6 million Chinese with adult-onset type 1 diabetes (10). While there is a wide range in the incidence of type 1 diabetes across different ethnic groups, even using differing methods of case identification (7), these data support the notion that, worldwide, over half of all new-onset type 1 diabetes cases occur in adults.

Natural History Studies of Type 1 Diabetes

Our understanding of the natural history of type 1 diabetes has been informed by a number of longitudinal and cross-sectional studies. At one end of the spectrum are prospective birth cohort studies, such as the BABYDIAB study in Germany and The Environmental Determinants of Diabetes in the Young (TEDDY) study, which includes sites in Germany, Finland, Sweden, and the U.S. While these studies now have the potential to explore the pathogenesis of islet autoimmunity by being extended into adulthood, they have primarily focused on events occurring in childhood (11). Clinical centers in North America, Europe, and Australia collaborate within Type 1 Diabetes TrialNet, a study that identifies autoantibody-positive adults and children in a cross-sectional manner to examine the pathogenesis of type 1 diabetes and to perform clinical trials on those at high risk in order to preserve β-cell function (12). At the other end of the spectrum, the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study is a case-cohort study nested in the U.K. prospective adult population-based EPIC study (13), while the clinical, immunogenetic, and metabolic characteristics of autoimmune adult-onset type 1 diabetes have been extensively studied in large American, European, and Chinese studies, including UK Prospective Diabetes Study (UKPDS), Action LADA, Scandia, Non Insulin Requiring Autoimmune Diabetes (NIRAD), and LADA China (9,14–19). Based on these cross-sectional and prospective studies, considerable data have been generated to define differences within type 1 diabetes according to the age at onset. Here, we highlight key aspects of age-related genetic, immune, and metabolic heter-ogeneity in type 1 diabetes. Of note, the term latent autoimmune diabetes in adults (LADA) has been used to describe adults with slowly progressive autoimmunity, sometimes exhibiting features overlapping with those of type 2 diabetes (9,14,18). At the outset of the workshop and for the purposes of this Perspective, LADA was not considered a unique entity; rather, we considered the classification of type 1 diabetes to include all individuals with evidence of autoimmunity, regardless of the trajectory of disease development (i.e., rapid or slowly progressive) or other associated demographic and/or clinical features (e.g., obesity).

Age-Related Genetic Heterogeneity

Type 1 diabetes shows heterogeneity across a broad range of clinical, genetic, immune, histological, and metabolic features (20). Childhood-onset type 1 diabetes is most often attributed to susceptibility alleles in human leukocyte antigen (HLA), which contribute ∼50% of the disease heritability. Whereas ethnic differences exist, notably for specific HLA genotypes, several broad principles apply. Compared with childhood-onset disease, adult-onset type 1 diabetes cases show lower type 1 diabetes concordance rates in twins (21), less high-risk HLA heterozygosity (19), lower HLA class I (14), more protective genotypes (14,15), and lower GRS (6,22), which are calculated by summing the odds ratios (OR) for disease-risk alleles.

Diabetes-Associated Immune Changes

Adult-onset type 1 diabetes, like childhood-onset type 1 diabetes, is associated with the presence of serum autoantibodies against β-cell antigens. Serum glutamic acid decarboxylase (GADA) autoantibodies may be useful as a predictor of type 1 diabetes in adults, as adult-onset cases most often present with GADA positivity (9,10,15,17,18,20,22) and possess an HLA-DR3 genotype (9,14,15, 20,21,23). In one prospective study of a general population, the hazard risk of incident diabetes in those with a high type 1 diabetes GRS and GADA positivity was 3.23 compared with all other individuals, suggesting that 1.8% of incident diabetes in adults was attributable to that combination of risk factors (13). In adult-onset type 1 diabetes, multiple diabetes-associated autoantibodies tend to be less prevalent with increasing age at diagnosis (1,8), yet GADA

remains the dominant autoantibody irrespective of the need for insulin treatment at diagnosis and irrespective of ethnicity (9,17,18,24,
25), even despite a paucity of HLA DR3, as in Japan and China (17,18). In contrast, childhood-onset type 1 diabetes cases often have insulin autoantibodies and an HLA-DR4 genotype, higher identical twin disease concordance, more HLA heterozygosity, and higher GRS (20). Taken together, these data indicate that type 1 diabetes is heterogeneous across the spectrum of diagnoses, suggesting that pathogenesis and optimal therapy are also diverse.

Data from the TrialNet Pathway to Prevention cohort demonstrated lower risk of progression to type 1 diabetes in adults than children, even when both show multiple autoantibodies on a single occasion and are monitored over 10 years (12). One recent analysis found that the 5-year rate of progression to diabetes in multiple autoantibody–positive adults was only ~15%, with a number of them remaining diabetes-free for decades (26). A combined cohort study, known as the Slow or Nonprogressive Autoimmunity to the Islets of Langerhans (SNAIL) study, is following such "slow progressors" with multiple autoantibodies who have yet to progress to stage 3 type 1 diabetes (i.e., clinical diagnosis) over at least a 10-year period (27). Many of these slow progressors lose disease-associated autoantibodies over time, adding complexity to cross-sectional classification (28). Based on estimates from natural history studies, slow progressors, even if identified when young, cannot account for all autoimmune adult-onset diabetes, indicating that autoantibodies must develop at all ages (11). However, little is known about those who initially develop autoimmunity as adults, mostly due to the lack of longitudinal studies focusing on this population.

People with type 1 diabetes, in contrast to the majority of those with type 2 diabetes, have altered adaptive immunity (i.e., islet autoantibodies and T-cell activation), while innate immune changes, including cytokine changes, are common to both (29). Increased T-cell activation by islet proteins has also been found in a proportion of adults with initially non-insulin-requiring diabetes, even when they lack diabetes autoantibodies (30). However, there is a paucity of immune studies on adult-onset type 1 diabetes and few histologic studies. An analysis of tissues from the Network for Pancreatic Organ Donors with Diabetes (nPOD) showed no relationship between age at diabetes onset and the frequency of islet insulitis (31). The composition of islet insulitis differs in very young children compared with older individuals, with the former having an increased frequency of B cells in islet infiltrates (32). However, relating pancreatic histological changes to changes in peripheral blood remains a challenge.

Adults with new-onset type 1 diabetes are at increased risk of other autoimmune conditions. About 30% of individuals with adult-onset type 1 diabetes have thyroid autoimmunity (27,29). In addition, adults with type 1 diabetes who possess high-titer GADA and/or multiple islet autoantibodies are at increased risk of progression to hypothyroidism (24,33). In a large population-based Chinese study, the prevalence of adult-onset type 1 diabetes was 6% among initially non-insulin-requiring diabetes cases, and 16.3% of them had thyroid autoimmunity (OR 2.4) (10). Of note, those with islet antigen 2 autoantibodies had a high risk of tissue transglutaminase autoantibodies, a marker for celiac disease (OR 19.1) (10). Thus, in the clinical setting, there should be a high index of suspicion for other autoimmune conditions in individuals with adult-onset type diabetes, and associated autoimmunity should be screened where clinically indicated.

Metabolic Characteristics of Adult-Onset Type 1 Diabetes

Age-related differences in type 1 diabetes extend to metabolic parameters. C-peptide at diagnosis is higher in adults than children, driven in part by higher BMI (34). Analysis of U.K., TrialNet, and Chinese cohorts has identified two distinct phases of C-peptide decline in stage 3 disease: an initial exponential fall followed by a period of relative stability. Along with initial differences at the time of clinical diagnosis, the rate of decline over 2–4 years was inversely related to age at onset (10,34–36). Furthermore, the U.S. T1D Exchange Study found that glycemic control was better in adults with type 1 diabetes than in children and adolescents with type 1 diabetes (37). The American Diabetes Association (ADA) targets for glycemia are higher in children, so that in this same cohort, 17% of children, compared with 21% of adults, achieved the ADA hemoglobin A_{1c} (HbA_{1c}) goal of $<7.5\%$ and $<7.0\%$, respectively (37). Other factors confound this relationship between age at diagnosis and metabolic control. First, individuals with adult-onset type 1 diabetes are more likely to have residual insulin-producing β-cells and persistent measurable C-peptide in disease of long duration, the latter of which has been linked to improved glycemic control (38,39). Second, individuals with adult-onset type 1 diabetes, initially not on insulin therapy, tend to have worse metabolic control than people with type 2 diabetes, even when receiving insulin treatment (9,40). The sole exception is the LADA China study, where worse control was noted only among those with a high GAD titer (18). Metabolic differences between adults and children extend beyond C-peptide. Adults with autoantibody positivity who progressed to type 1 diabetes were less likely than very young children to exhibit elevated proinsulin/C-peptide ratios prior to stage 3 disease onset (41). In addition, in individuals with disease of long duration, those diagnosed at an older age had evidence of improved proinsulin processing and nutrient-induced proinsulin secretory capacity (42).

Diagnosis and Management of Adult-Onset Type 1 Diabetes

Correctly identifying diabetes etiology and type is difficult, and misclassification may occur in up to 40% of adults presenting with type 1 diabetes (1,2). Reasons underlying misclassification are multiple and include *1*) lack of awareness that the onset of type 1 diabetes is not limited to children; *2*) the overwhelming majority of people developing diabetes as older adults have type 2 diabetes, contributing to a confirmation bias (2); *3*) typical clinical criteria, such as BMI and metabolic syndrome, can be poor discriminators, especially as rates of obesity in the overall population increase (9,43); *4*) clinical characteristics of adult-onset type 1 diabetes can masquerade as type 2 diabetes, given their slow metabolic progression and risk of metabolic syndrome (which occurs in about 40%), so that the distinction between types of diabetes may be

blurred (43–45); and *5*) lack of awareness of and accessibility to biomarkers that may serve as tools to distinguish type 1 diabetes and type 2 diabetes.

Tools to distinguish type 1 and type 2 diabetes are under active development. For example, classification models integrating up to five prespecified predictor variables, including clinical features (age of diagnosis and BMI) and clinical biomarkers (autoantibodies and GRS) in a White European population, had high accuracy to identify adults with recently diagnosed diabetes with rapid insulin requirement despite using GRS derived from childhood-onset type 1 diabetes. While GRS have the potential to assist diagnosis of type 1 diabetes in uncertain cases, they are not yet widely available in clinical practice. Moreover, it is important to note that while the model was optimized with the inclusion of all five variables, the addition of GRS had only a modest effect on overall model performance (22).

Classification can be aided by the measurement of autoantibodies and C-peptide. Recommended autoantibodies to assay at the time of diagnosis include those to insulin (insulin autoantibody), glutamate decarboxylase isoform 65 (GAD65A), insulinoma antigen 2, and zinc transporter isoform 8 (Znt8A), with GAD65A being the most prevalent autoantibody among adults. High levels or the presence of more than one antibody increases the likelihood of type 1 diabetes. However, it is important to realize that islet autoantibodies are a continuous marker that can also occur in the population without diabetes. As with many other tests, an abnormal test is usually based on a threshold signal from control populations without diabetes, usually the 97.5th or the 99th centile. Therefore, false-positive results with these assays can occur and can be reduced by using higher-specificity assays or thresholds and targeting testing toward those with clinical features suggestive of type 1 diabetes (46). Finally, since antibody levels can wane over time in established type 1 diabetes, the absence of autoantibodies does not rule out the possibility of a diagnosis of type 1 diabetes.

Measurement of C-peptide, paired with a blood glucose in the same sample, provides an estimate of endo-genous insulin production and has the most utility in disease of long duration when levels fall below 300 pmol/L (39,47). However, C-peptide levels are typically higher at presentation and may be difficult to distinguish from levels in type 2 diabetes, which are usually >600 pmol/L. Thus, thresholds of C-peptide that clearly delineate type 1 diabetes from type 2 diabetes at diagnosis cannot be categorically defined, and C-peptide must be interpreted within the context of other clinical and laboratory features. Measurement of a random nonfasting C-peptide is superior to fasting C-peptide in identifying type 1 diabetes (48) and is well correlated with stimulated C-peptide levels measured during a mixed-meal tolerance test, which is considered the gold standard assessment of insulin secretory function in established type 1 diabetes (49). A recent analysis found that concomitant blood glucose ≥144 mg/dL (8 mmol/L) increased the specificity of random C-peptide in predicting a stimulated C-peptide level <600pmol/L, suggesting this is a reasonable threshold of blood glucose to employ for C-peptide interpretation (49).

C-peptide also can be used to guide therapy (50). Individuals with a random C-peptide level ≤300 pmol/L should be managed mainly with insulin. For those with random C-peptide levels >300 pmol/L, insulin could be combined with other diabetes therapies, although evidence about safety and efficacy is limited. It is generally agreed that sulfonylureas should be avoided because of the potential to hasten β-cell failure (50). There is concern for increased risk of diabetic ketoacidosis (DKA) with sodium–glucose cotransporter 1 (SGLT1) and SGLT2 inhibitors when these agents are used in type 1 diabetes, especially in nonobese individuals who may need only low dosages of insulin (51). All other agents could be considered for therapy in those not requiring insulin initially. In individuals with random C-peptide levels exceeding 600 pmol/L, management can be much as recommended for type 2 diabetes, with the caveats outlined above (50). An important consideration is that loss of β-cell function may be rapid in autoimmune diabetes. As such, individuals treated without insulin should be closely monitored.

In the absence of prospectively validated decision support tools that have been tested in multiethnic populations, we suggest, as an approach to aid the practicing physician, assessment of age, autoimmunity, body habitus/BMI, background, control, and comorbidities, using the acronym AABBCC (Table 2). This approach includes the clinical consideration of autoimmunity and other clinical features suggestive of type 1 diabetes, including age at diagnosis, low BMI, an unexplained or rapid worsening of clinical course manifesting as a lack of response or rising HbA_{1c} with type 2 diabetes medications, and a rapid requirement for insulin therapy, especially within 3 years of diagnosis. It should be emphasized that among these features, age at diagnosis (<40 years), low BMI (<25 kg/m^2), and rapid need for insulin therapy are the most discriminatory (43). We recommend measurement of islet antibodies and C-peptide be considered in all older people with clinical features that suggest type 1 diabetes, with islet autoantibodies being the initial test of choice in short-duration disease (<3 years) and C-peptide the test of choice at longer durations.

Diabetes-Associated Comorbidities and Complications

DKA

The U.S. SEARCH for Diabetes in Youth study reported that nearly 30% of youth with newly diagnosed type 1 diabetes age <20 years presented with DKA (52). The frequency of DKA among adults at diagnosis with type 1 diabetes is unknown but is believed to be lower given that they often have higher C-peptide levels at diagnosis and a slower decline in β-cell function over time, even in those requiring insulin initially (34). Among childhood-onset type 1 diabetes, most episodes of DKA beyond diagnosis are associated with insulin omission, pump failure, or treatment error (53). However, for adults with type 1 diabetes, the primary risk factors are noncompliance and infections (54), the former sometimes due to the cost of insulin (55). Thus, there is a need to further understand DKA in adults, not least because it is associated with long-term worsening glycemic control (56).

Hypoglycemia

Fear of hypoglycemia remains a major problem in the clinical management of adults with type 1 diabetes (57),

influencing quality of life and glycemic control. The effect of diabetes duration or age at diagnosis on hypoglycemia risk is not consistent among different studies. However, α-cell responses to hypoglycemia and hypoglycemia risk are both lower in individuals with higher C-peptide levels (38). Because residual C-peptide is more likely to be observed in those with a later age of onset, hypoglycemia risk may be different between those with childhood- and adult-onset diabetes. While insulin pumps and continuous glucose monitors are associated with improved glycemic control and reduced hypoglycemia (37), adults may show reluctance or inertia in adopting newer technologies. In the T1D Exchange study population, 63% of adults used an insulin pump while only 30% used a continuous glucose monitor, and use of these technologies tended to be lower in adults than in children (37). Factors that dictate use of these technologies are multiple and may include reduced access to or acceptance of wearable technology, challenges with insurance coverage, especially in the context of past misclassification, and/or inadequate education about hypoglycemia risk (58). A better understanding of potential barriers to technology use in adult-onset type 1 diabetes is needed. Furthermore, little is known about changes in hypoglycemia risk across the life span of individuals with adult-onset disease, representing an important gap in knowledge.

Microvascular and Macrovascular Disease Complications

Despite the prevalence of adult-onset type 1 diabetes, there is a paucity of data on the burden of microvascular complications in this population. Current knowledge is largely based on small, cross-sectional studies. In aggregate, these studies suggest that the prevalence of nephropathy and retinopathy are lower in adult-onset type 1 than in type 2 diabetes, but this conclusion is potentially confounded by diabetes duration. For example, the prevalence of nephropathy and retinopathy was lower in Chinese individuals with adult-onset type 1 diabetes than in those with type 2, but only in those with a disease duration <5 years, while in the Botnia Study, retinopathy risk in adult-onset type 1 diabetes increased, as expected, with disease duration (59). Two substantial prospective studies recently reported that those adults with diabetes enrolled in the UKPDS who were also GADA positive (i.e., presumably with type 1 diabetes) compared with those who were GADA negative (with type 2 diabetes) showed a higher prevalence of retinopathy and lower prevalence of cardiovascular

Table 1—Knowledge gaps

Area of focus	Description
Eliminating cultural bias in order to understand what impacts disease development	Most large-scale studies of adult type 1 diabetes have been done in Europe, North America, and China. There is a pressing need to extend these studies to other continents and to diverse racial and ethnic groups. Such studies could help us identify and understand the nature and implications of diversity, whether in terms of pathogenesis, cultural differences, or health care disparity. In addition, prospective childhood studies of high-risk birth cohorts could be extended into adulthood and new studies initiated to better understand mechanisms behind disease development and whether there is a differentiation in the disease process between young and adult type 1 diabetes.
Population screening	At present, universal childhood screening programs are being developed in many countries. Research will be needed to develop strategies for the follow-up of autoantibody-positive populations throughout adulthood.
Disease-modifying therapies in early-stage disease	Trials of disease-modifying therapies have generally shown better efficacy in children (12). There are likely to be important differences in agent selection between adult and pediatric populations, and these differences require study.
Diagnosis and misclassification	There is a need to build a diagnostic decision tree to aid in diabetes classification. Tools are needed to estimate individual-level risk.
Adjunctive therapies	There is a need to better understand the benefits and risks of using therapies that are adjunctive to insulin in adult-onset type 1 diabetes. To this end, large-scale drug trials need to be performed, and therapeutic decision trees are required to help health care professionals and endocrinologists select such therapies.
Post-diagnosis education and support	Improving education and support post-diagnosis is vital and should include psychosocial support, health care provision, and analysis of long-term outcomes (including complications) in adult-onset type 1 diabetes. Current knowledge is limited with respect to complications, especially related to the complex mechanisms contributing to macrovascular disease in adult-onset type 1 diabetes. Surveillance efforts based on larger and representative cohorts of patients with clear and consistent case definitions are needed to better understand the burden and risk of diabetes-related chronic complications in this large population.

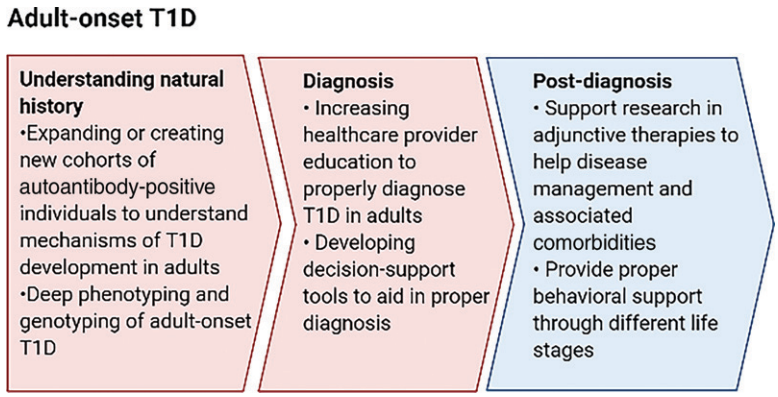

Figure 1—Proposed roadmap to better understand, diagnose, and care for adults with type 1 diabetes (T1D). Created in BioRender (BioRender.com).

events (60,61). These results are consistent with people with adult-onset type 1 diabetes compared with those with type 2 diabetes, showing a general tendency to higher HbA_{1c} levels (40,44,60,61) as well as reduced traditional cardiovascular risk factors, including reduced adiposity (BMI and waist circumference), metabolic (lipid levels), and vascular (blood pressure) profiles (9,24,62). Nevertheless, all-cause mortality and cardiovascular mortality rates in such individuals with adult-onset type 1 diabetes (59) are still higher than those among individuals without diabetes. In addition, there are discrepancies across studies, likely related to differences in populations under study (i.e., age, race/ethnicity, and diabetes duration), lack of consistent case definitions (i.e., adult-onset type 1 diabetes or LADA cases), and different outcomes, as well as small sample sizes with insufficient events on which to base strong recommendations.

Psychosocial Challenges

Negative stressors, including pressure to achieve target HbA_{1c} levels, lifestyle considerations, and fear of complications, are factors leading to the increased frequency of mood disorders, attempted suicide, and psychiatric care in adults with diabetes (63). In individuals who have experienced misclassification, additional stress derives from conflicting messages about the nature of their diabetes. Among adults with type 1 diabetes, those with high psychological coping skills (e.g., self-efficacy, self-esteem, and optimism) and adaptive skills may buffer the negative effect of stress and should be cultivated (64). Relationship challenges, including sexual intimacy, starting a family, caring for children, and relational stress, are major stressors for adults with type 1 diabetes (65). In addition, there is the looming threat of complications, including blindness and amputations (65). Adults with type 1 diabetes describe a sense of powerlessness, fear of hypoglycemia, and the challenges of both self-management and appropriate food management (66). A common misunderstanding is that while they face the same life choices associated with type 2 diabetes (e.g., weight loss, exercise, and limiting intake of simple sugars), adults with type 1 diabetes may require different management skills (67). Moreover, there is a strong association in adults with type 1 diabetes between chronic, stressful life events and fluctuating HbA_{1c}, possibly due to indirect mechanisms, including adherence to diabetes management (68). Whether these risks differ between those diagnosed as children or as adults is unclear and requires additional study.

CLOSING

In this Perspective, we have summarized the current understanding of adult-onset type 1 diabetes while identifying many knowledge gaps (Table 1). Epidemiological data from diverse ethnic groups show that adult-onset type 1 diabetes is often more prevalent than childhood-onset type 1 diabetes. However, our understanding of type 1 diabetes presenting in adults is limited. This striking shortfall in knowledge (Table 1) results in frequent misclassification, which may negatively impact disease management. Here, we outline a roadmap for addressing these deficiencies (Fig. 1). A cornerstone of this roadmap is a renewed emphasis on the careful consideration of the underlying etiology of diabetes in every adult presenting with diabetes.

In the absence of data-driven classification tools capable of estimating individual-level risk, we offer a simple set of questions, incorporating what we have termed the AABBCCs of diabetes classification and management (Table 2). In parallel, we invite the research community to join together in addressing key gaps in knowledge through studies aimed at defining the genetic, immunologic, and metabolic phenotype of adult-onset type 1 diabetes with the goal of using this

Table 2—AABBCC approach to diabetes classification

Parameter	Description
Age	Autoimmune diabetes is most prevalent in patients aged <50 years at diagnosis. Those aged <35 years at diagnosis should be considered for maturity-onset diabetes of the young as well as type 1 diabetes
Autoimmunity	Does this individual have islet autoantibodies or a history of autoimmunity (i.e., thyroid disease, celiac disease)? Is there a goiter or vitiligo on exam?
Body habitus/BMI	Is the body habitus or BMI inconsistent with a diagnosis of type 2 diabetes, especially if BMI <25 kg/m^2?
Background	What is the patient's background? Is there a family history of autoimmunity and/or type 1 diabetes? Are they from a high-risk ethnic group?
Control	Are diabetes control and HbA_{1c} worsening on noninsulin therapies? Has there been an accelerated change in HbA_{1c}? Is the C-peptide low, that is, ≤300 pmol/L (especially <200 pmol/L), or is there clinical evidence that β-cell function is declining? Was there a need for insulin therapy within 3 years of diabetes diagnosis?
Comorbidities	Irrespective of immunogenetic background, coexistent cardiac or renal disease and their risk factors impact the approach to therapy and HbA_{1c} targets.

knowledge to develop improved approaches for disease management and prevention (Fig. 1).

Acknowledgments. Sharon Saydah, Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, attended the workshop and participated in subsequent discussions of the manuscript. Elizabeth Seaquist, Division of Diabetes, Endocrinology, and Metabolism at the University of Minnesota, participated in the workshop. The authors acknowledge Marilyn L. Wales for her assistance with formatting the manuscript.

Funding and Duality of Interest. This manuscript is the result of a one-day meeting held at JDRF headquarters in New York, NY. Financial support for the workshop was provided by JDRF and Janssen Research and Development, LLC. Financial support from Janssen Research and Development, LLC, for the workshop was in an unrestricted grant to JDRF. JDRF provided participants with transportation, lodging, and meals to attend the workshop. No additional support was provided for the writing of the manuscript. R.D.L. is supported by a grant from the European Union (contract no. QLGi-CT-2002-01886). C.E.-M. is supported by National Institute for Health Research grants R01 DK093954, R21DK119800, U01DK127786, R01DK127308, and P30DK097512; VA Merit Award I01BX001733; JDRF grant 2-SRA-2019-834-S-B; and gifts from the Sigma Beta Sorority, the Ball Brothers Foundation, and the George and Frances Ball Foundation. R.B. is supported in part by the Italian Ministry of University and Research (project code 20175L9H7H). A.G.J. is funded by a National Institute for Health Research (NIHR) Clinician Scientist fellowship (CS-2015-15-018). L.S.P. is supported in part by U.S. Department of Veterans Affairs (VA) awards CSP #2008, I01 CX001899, I01 CX001737, and Health Services Research & Development IIR 07-138; National Institute for Health Research awards R21 DK099716, R18 DK066204, R03 AI133172, R21 AI156161, U01 DK091958, U01 DK098246, and UL1 TR002378; and Cystic Fibrosis Foundation award PHILLI12A0.

R.D.L. received unrestricted educational grants from Novo Nordisk, Sanofi, MSD, and AstraZeneca. C.E.-M. has participated in advisory boards for Dompé Pharmaceuticals, Provention Bio, MaiCell Technologies, and ISLA Technologies. C.E.M. is the recipient of in-kind research support from Nimbus Pharmaceuticals and Bristol Myers Squibb and an investigator-initiated research grant from Eli Lilly and Company. J.F.-B. and J.L.D. were employed by JDRF during the workshop and early stages of writing. J.F.-B. is currently an employee of Provention Bio, and J.L.D. is currently an employee of Janssen Research and Development, LLC. R.B. participated in advisory boards for Sanofi and Eli Lilly and received honoraria for speaker bureaus from Sanofi, Eli Lilly, AstraZeneca, Novo Nordisk, and Abbott. L.S.P. has served on scientific advisory boards for Janssen and has or had research support from Merck, Pfizer, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, AbbVie, Vascular Pharmaceuticals, Janssen, GlaxoSmithKline, and the Cystic Fibrosis Foundation. L.S.P. is also a cofounder and officer and board member and stockholder for a company, Diasyst, Inc., that markets software aimed to help improve diabetes management. No other potential conflicts of interest relevant to this article were reported.

The sponsors had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript. This work is not intended to reflect the official opinion of the VA or the U.S. Government.

Author Contributions. R.D.L., C.E.M., J.F.-B., and J.L.D. conceived of the article and wrote and edited the manuscript. All other authors were involved in the writing and editing of the manuscript. R.D.L. and C.E.-M. are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Muñoz C, Floreen A, Garey C, et al. Misdiagnosis and diabetic ketoacidosis at diagnosis of type 1 diabetes: patient and caregiver perspectives. Clin Diabetes 2019;37:276–281
2. Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. Diabetologia 2019;62:1167–1172
3. Thunander M, Petersson C, Jonzon K, et al. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes Res Clin Pract 2008;82:247–255
4. Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Med 2017;15:199
5. Weng J, Zhou Z, Guo L, et al.; T1D China Study Group. Incidence of type 1 diabetes in China, 2010-13: population based study. BMJ 2018;360:j5295
6. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol 2018;6:122–129
7. Diaz-Valencia PA, Bougnères P, Valleron AJ. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. BMC Public Health 2015;15:255
8. Gorham ED, Barrett-Connor E, Highfill-McRoy RM, et al. Incidence of insulin-requiring diabetes in the US military. Diabetologia 2009;52:2087–2091
9. Hawa MI, Kolb H, Schloot N, et al.; Action LADA Consortium. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care 2013;36:908–913
10. Xiang Y, Huang G, Zhu Y, et al.; China National Diabetes and Metabolic Disorders Study Group. Identification of autoimmune type 1 diabetes and multiple organ-specific autoantibodies in adult-onset non-insulin-requiring diabetes in China: a population-based multicentre nationwide survey. Diabetes Obes Metab 2019;21:893–902
11. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479
12. Wherrett DK, Chiang JL, Delamater AM, et al.; Type 1 Diabetes TrialNet Study Group. Defining pathways for development of disease-modifying therapies in children with type 1 diabetes: a consensus report. Diabetes Care 2015;38:1975–1985
13. Rolandsson O, Hampe CS, Sharp SJ, et al. Autoimmunity plays a role in the onset of diabetes after 40 years of age. Diabetologia 2020;63:266–277
14. Mishra R, Åkerlund M, Cousminer DL, et al. Genetic discrimination between LADA and childhood-onset type 1 diabetes within the MHC. Diabetes Care 2020;43:418–425
15. Zhu M, Xu K, Chen Y, et al. Identification of novel T1D risk loci and their association with age and islet function at diagnosis in autoantibody-positive T1D individuals: based on a two-stage genome-wide association study. Diabetes Care 2019;42:1414–1421
16. Buzzetti R, Di Pietro S, Giaccari A, et al.; Non Insulin Requiring Autoimmune Diabetes Study Group. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. Diabetes Care 2007;30:932–938
17. Yasui J, Kawasaki E, Tanaka S, et al.; Japan Diabetes Society Committee on Type 1 Diabetes Mellitus Research. Clinical and genetic characteristics of non-insulin-requiring glutamic acid decarboxylase (GAD) autoantibody-positive diabetes: a nationwide survey in Japan. PLoS One 2016;11:e0155643
18. Zhou Z, Xiang Y, Ji L, et al.; LADA China Study Group. Frequency, immunogenetics, and clinical characteristics of latent autoimmune diabetes in China (LADA China study): a nationwide, multicenter, clinic-based cross-sectional study. Diabetes 2013;62:543–550
19. Howson JM, Rosinger S, Smyth DJ, Boehm BO; ADBW-END Study Group. Genetic analysis of adult-onset autoimmune diabetes. Diabetes 2011;60:2645–2653
20. Battaglia M, Ahmed S, Anderson MS, et al. Introducing the endotype concept to address the challenge of disease heterogeneity in type 1 diabetes. Diabetes Care 2020;43:5–12
21. Redondo MJ, Yu L, Hawa M, et al. Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetologia 2001;44:354–362
22. Lynam A, McDonald T, Hill A, et al. Development and validation of multivariable clinical diagnostic models to identify type 1 diabetes requiring rapid insulin therapy in adults aged 18-50 years. BMJ Open 2019;9:e031586
23. Cousminer DL, Ahlqvist E, Mishra R, et al.; Bone Mineral Density in Childhood Study. First genome-wide association study of latent autoimmune diabetes in adults reveals novel insights linking immune and metabolic diabetes. Diabetes Care 2018;41:2396–2403
24. Zampetti S, Capizzi M, Spoletini M, et al.; NIRAD Study Group. GADA titer-related risk for organ-specific autoimmunity in LADA subjects subdivided according to gender (NIRAD study 6). J Clin Endocrinol Metab 2012;97:3759–3765
25. Balcha SA, Demisse AG, Mishra R, et al. Type 1 diabetes in Africa: an immunogenetic study in the Amhara of North-West Ethiopia. Diabetologia 2020;63:2158–2168

26. Jacobsen LM, Bocchino L, Evans-Molina C, et al. The risk of progression to type 1 diabetes is highly variable in individuals with multiple autoantibodies following screening. Diabetologia 2020;63:588–596
27. Long AE, Wilson IV, Becker DJ, et al. Characteristics of slow progression to diabetes in multiple islet autoantibody-positive individuals from five longitudinal cohorts: the SNAIL study. Diabetologia 2018;61:1484–1490
28. Hanna SJ, Powell WE, Long AE, et al. Slow progressors to type 1 diabetes lose islet autoantibodies over time, have few islet antigen-specific $CD8^{+}$ T cells and exhibit a distinct $CD95^{hi}$ B cell phenotype. Diabetologia 2020;63:1174–1185
29. Schloot NC, Pham MN, Hawa MI, et al.; Action LADA Group. Inverse relationship between organ-specific autoantibodies and systemic immune mediators in type 1 diabetes and type 2 diabetes: Action LADA 11. Diabetes Care 2016;39:1932–1939
30. Brooks-Worrell BM, Palmer JP. Setting the stage for islet autoimmunity in type 2 diabetes: obesity-associated chronic systemic inflammation and endoplasmic reticulum (ER) stress. Diabetes Care 2019;42:2338–2346
31. Campbell-Thompson M, Fu A, Kaddis JS, et al. Insulitis and β-cell mass in the natural history of type 1 diabetes. Diabetes 2016;65:719–731
32. Leete P, Willcox A, Krogvold L, et al. Differential insulitic profiles determine the extent of β-cell destruction and the age at onset of type 1 diabetes. Diabetes 2016;65:1362–1369
33. Fleiner HF, Bjøro T, Midthjell K, Grill V, Åsvold BO. Prevalence of thyroid dysfunction in autoimmune and type 2 diabetes: the population-based HUNT study in Norway. J Clin Endocrinol Metab 2016;101:669–677
34. Greenbaum CJ, Beam CA, Boulware D, et al.; Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61:2066–2073
35. Gong S, Wu C, Zhong T, et al. Complicated curve association of body weight at diagnosis with C-peptide in children and adults with new-onset type 1 diabetes. Diabetes Metab Res Rev 2020;36:e3285
36. Hao W, Gitelman S, DiMeglio LA, Boulware D; Type 1 Diabetes TrialNet Study Group. Fall in c-peptide during first 4 years from diagnosis of type 1 diabetes: variable relation to age, HbA1c, and insulin dose. Diabetes Care 2016;39:1664–1670
37. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. Diabetes Technol Ther 2019;21:66–72
38. Rickels MR, Evans-Molina C, Bahnson HT, et al.; T1D Exchange β-Cell Function Study Group. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. J Clin Invest 2020;130:1850–1862
39. Davis AK, DuBose SN, Haller MJ, et al.; T1D Exchange Clinic Network. Prevalence of detectable C-peptide according to age at diagnosis and duration of type 1 diabetes. Diabetes Care 2015;38:476–481
40. Andersen CD, Bennet L, Nyström L, et al. Worse glycaemic control in LADA patients than in those with type 2 diabetes, despite a longer time on insulin therapy. Diabetologia 2013;56:252–258
41. Sims EK, Chaudhry Z, Watkins R, et al. Elevations in the fasting serum proinsulin-to-C-peptide ratio precede the onset of type 1 diabetes. Diabetes Care 2016;39:1519–1526
42. Sims EK, Bahnson HT, Nyalwidhe J, et al.; T1D Exchange Residual C-Peptide Study Group. Proinsulin secretion is a persistent feature of type 1 diabetes. Diabetes Care 2019;42:258–264
43. Shields BM, Peters JL, Cooper C, et al. Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. BMJ Open 2015;5:e009088
44. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361–369
45. Hawa MI, Thivolet C, Mauricio D, et al.; Action LADA Group. Metabolic syndrome and autoimmune diabetes: action LADA 3. Diabetes Care 2009;32:160–164
46. Jones AG, McDonald TJ, Shields BM, Hagopian W, Hattersley AT. Latent autoimmune diabetes of adults (LADA) is likely to represent a mixed population of autoimmune (type 1) and nonautoimmune (type 2) diabetes. Diabetes Care 2021dc202834
47. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med 2013;30:803–817
48. Berger B, Stenström G, Sundkvist G. Random C-peptide in the classification of diabetes. Scand J Clin Lab Invest 2000;60:687–693
49. Hope SV, Knight BA, Shields BM, Hattersley AT, McDonald TJ, Jones AG. Random non-fasting C-peptide: bringing robust assessment of endogenous insulin secretion to the clinic. Diabet Med 2016;33:1554–1558
50. Buzzetti R, Tuomi T, Mauricio D, et al. Management of latent autoimmune diabetes in adults: a consensus statement from an international expert panel. Diabetes 2020;69:2037–2047
51. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care 2019;42:1147–1154
52. Dabelea D, Rewers A, Stafford JM, et al.; SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014;133:e938–e945
53. Rewers A. Acute metabolic complications in diabetes. In *Diabetes in America*. 3rd ed. Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases, 2018; pp. 1–19
54. Umpierrez GE, Kitabchi AE. Diabetic ketoacidosis: risk factors and management strategies. Treat Endocrinol 2003;2:95–108
55. Randall L, Begovic J, Hudson M, et al. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. Diabetes Care 2011;34:1891–1896
56. Duca LM, Reboussin BA, Pihoker C, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: the SEARCH for diabetes in youth study. Pediatr Diabetes 2019;20:172–179
57. Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, Nemeth J, Quinn L. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention – a review. J Diabetes Complications 2016;30:167–177
58. Engler R, Routh TL, Lucisano JY. Adoption barriers for continuous glucose monitoring and their potential reduction with a fully implanted system: results from patient preference surveys. Clin Diabetes 2018;36:50–58
59. Isomaa B, Almgren P, Henricsson M, et al. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). Diabetes Care 1999;22:1347–1353
60. Maddaloni E, Coleman RL, Agbaje O, Buzzetti R, Holman RR. Time-varying risk of microvascular complications in latent autoimmune diabetes of adulthood compared with type 2 diabetes in adults: a post-hoc analysis of the UK Prospective Diabetes Study 30-year follow-up data (UKPDS 86). Lancet Diabetes Endocrinol 2020;8:206–215
61. Maddaloni E, Coleman RL, Pozzilli P, Holman RR. Long-term risk of cardiovascular disease in individuals with latent autoimmune diabetes in adults (UKPDS 85). Diabetes Obes Metab 2019;21:2115–2122
62. Tuomi T, Carlsson A, Li H, et al. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999;48:150–157
63. Robinson ME, Simard M, Larocque I, Shah J, Nakhla M, Rahme E. Risk of psychiatric disorders and suicide attempts in emerging adults with diabetes. Diabetes Care 2020;43:484–486
64. Yi JP, Vitaliano PP, Smith RE, Yi JC, Weinger K. The role of resilience on psychological adjustment and physical health in patients with diabetes. Br J Health Psychol 2008;13:311–325
65. Trief PM, Sandberg JG, Dimmock JA, Forken PJ, Weinstock RS. Personal and relationship challenges of adults with type 1 diabetes: a qualitative focus group study. Diabetes Care 2013;36:2483–2488
66. Fisher L, Polonsky WH, Hessler DM, et al. Understanding the sources of diabetes distress in adults with type 1 diabetes. J Diabetes Complications 2015;29:572–577
67. Hilliard ME, Yi-Frazier JP, Hessler D, Butler AM, Anderson BJ, Jaser S. Stress and A1c among people with diabetes across the lifespan. Curr Diab Rep 2016;16:67
68. Lloyd CE, Dyer PH, Lancashire RJ, Harris T, Daniels JE, Barnett AH. Association between stress and glycemic control in adults with type 1 (insulin-dependent) diabetes. Diabetes Care 1999;22:1278–1283