Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association

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The Adoption of the Staging Classification System Is Endorsed by the American Association of Clinical Endocrinologists, the International Society for Pediatric and Adolescent Diabetes, and The Leona M. and Harry B. Helmsley Charitable Trust

Insights from prospective, longitudinal studies of individuals at risk for developing type 1 diabetes have demonstrated that the disease is a continuum that progresses sequentially at variable but predictable rates through distinct identifiable stages prior to the onset of symptoms. Stage 1 is defined as the presence of β-cell autoimmunity as evidenced by the presence of two or more islet autoantibodies with normoglycemia and is presymptomatic, stage 2 as the presence of β-cell autoimmunity with dysglycemia and is presymptomatic, and stage 3 as onset of symptomatic disease. Adoption of this staging classification provides a standardized taxonomy for type 1 diabetes and will aid the development of therapies and the design of clinical trials to prevent symptomatic disease, promote precision medicine, and provide a framework for an optimized benefit/risk ratio that will impact regulatory approval, reimbursement, and adoption of interventions in the early stages of type 1 diabetes to prevent symptomatic disease.

Type 1 diabetes is a chronic autoimmune disease with both genetic and environmental contributions that results over time in an immune-mediated loss of functional pancreatic β-cell mass, leading to symptomatic diabetes and lifelong insulin dependence (1–3). The disorder represents a disease continuum that begins prior to its symptomatic manifestations. The risk of developing symptomatic type 1 diabetes can be identified and quantified, the disease can be characterized into well-defined stages, and the rate of progression to symptomatic disease can be predicted with appreciable accuracy. The ability to screen for risk and to stage type 1 diabetes prior to symptomatic type 1 diabetes provides an opportunity to intervene to delay and ultimately to prevent the onset of clinical symptoms.

Herein, we propose a staging classification system that recognizes the earliest stages of human type 1 diabetes. Adoption of this staging classification will 1) provide a new standardized taxonomy for human type 1 diabetes; 2) accelerate the clinical development of therapies to prevent symptomatic disease; 3) aid the design of clinical trials through the use of risk profiles, subject stratification, and stage-specific clinical trial end points; 4) promote precision medicine involving the tailoring of optimal therapies to specific individuals at specific stages of the disease; subject stratification, and the work is not altered.

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disease; and 5) provide a framework and approach for an optimized benefit/risk ratio that should impact regulatory approval, reimbursement, and adoption of interventions in the early stages of type 1 diabetes to prevent symptomatic disease.

OVERVIEW OF STAGING OF TYPE 1 DIABETES

As originally proposed over 25 years ago, human type 1 diabetes arises from both genetic and environmental factors that lead to immune-mediated destruction of pancreatic β-cells and loss of β-cell function. After onset of islet autoimmunity, the disease progresses through a pre-symptomatic stage identified by markers of autoimmunity and glucose intolerance, or so-called dysglycemia, arising from further loss of β-cell function and culminates ultimately with clinical symptoms and signs of diabetes (1–3). In children and adults, the rate of progression from onset of β-cell autoimmunity to glucose intolerance and then to symptomatic disease is variable, lasting from months to decades (2,3).

Today, type 1 diabetes is typically diagnosed based on clinical symptomatology associated with overt hyperglycemia and metabolic imbalance. As detailed below, however, the disease can now be identified at earlier presymptomatic stages. Indeed, first- or second-degree relatives of individuals with type 1 diabetes or children identified from the general population are being screened for increased risk for developing type 1 diabetes in the research setting (4–6). Distinct asymptomatic stages of type 1 diabetes with prognostic implication have been identified, and prevention clinical trials are ongoing with enrollment criteria and end points based on specific disease stages.

As shown in Fig. 1 and as detailed below, a broad body of evidence supports a standardized classification of distinct early stages of type 1 diabetes with prognostic significance.

Stage 1: Autoimmunity+/ Normoglycemia/Presymptomatic Type 1 Diabetes

Stage 1 represents individuals who have developed two or more type 1 diabetes-associated islet autoantibodies but are normoglycemic. For children who were screened for genetic risk at birth and reach this stage, the 5-year and 10-year risks of symptomatic disease are approximately 44% and 70%, respectively, and the lifetime risk approaches 100% (7). The risk at this stage is quite similar in genetically at-risk children and in relatives of individuals with type 1 diabetes, as detailed below (7–9).

Stage 2: Autoimmunity+/ Dysglycemia/Presymptomatic Type 1 Diabetes

Stage 2, like stage 1, includes individuals with two or more islet autoantibodies but whose disease has now progressed to the development of glucose intolerance, or dysglycemia, from loss of functional β-cell mass. The 5-year risk of symptomatic disease at this stage is approximately 75%, and the lifetime risk approaches 100% (10).

Stage 3: Autoimmunity+/ Dysglycemia/Symptomatic Type 1 Diabetes

Stage 3 represents manifestations of the typical clinical symptoms and signs of diabetes, which may include polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis (DKA), and others.

PRE-STAGE 1: GENETIC SUSCEPTIBILITY AND GENETIC RISK DETECTION OF TYPE 1 DIABETES

The HLA region on chromosome 6 accounts for about 30–50% of the genetic risk of type 1 diabetes (11), with the greatest association with HLA class II haplotypes DRB1*0301-DQB1*0201 (DR3-DQ2) and DRB1*0401-DQB1*0302 (DR4-DQ8) (Table 1). The genotype associated with the highest risk for type 1 diabetes is the heterozygous DR3/4 genotype. HLA class II DRB1*1501 and DQA1*0102-DQB1*0602 confer disease resistance, at least in children younger than 12 years of age. The rising incidence of type 1 diabetes (12–14) has been accompanied by a decrease in the relative contribution from the highest risk HLA genotype (15,16).

The remaining genetic risk for type 1 diabetes can be attributed to the approximately 50 non-HLA genes or loci identified via candidate gene and genome-wide association study approaches, each with modest to small effects on disease risk. The highest non-HLA genetic contribution arises from the INS, PTPN22, CTLA4, and IL2RA genes, with the latter three genes also contributing to susceptibility to other autoimmune diseases (17). Non-HLA genetic contribution may be acting through immune regulation (18), although the recent demonstration of gene expression commonly in pancreatic islets and the alternative splicing of several of these gene products in cytokine-stimulated islets have raised the question of whether some of these genes may in part be acting in the β-cell (19).

Genetic variation likely influences both immune regulation and the host response to environmental etiologies, which determine an individual’s initial disease susceptibility and progression through sequential homeostatic checkpoints prior to onset of symptomatic disease. In fact, unlike the HLA type 1 diabetes susceptibility genes that appear to have a limited effect on the rate of progression to symptomatic disease after the onset of islet autoimmunity (20), several non-HLA type 1 diabetes susceptibility genes have been demonstrated to influence disease progression, including IL2, CD25, INS VNTR, IL18RAP, IL10, IFIH1, and PTPN22 (21). As a result, non-HLA single nucleotide polymorphisms and risk allele scores have been used to stratify risk for both developing islet autoantibodies and progressing from islet autoimmunity to symptomatic type 1 diabetes (22,23). With larger databases, this analysis will likely be refined and improved.

Multiple environmental factors have been invoked as contributing to the pathogenesis of type 1 diabetes, including, but not limited to, maternal and intrauterine environment, route of neonatal delivery, viruses, host microbiome, antibiotics, and food/diet (24–26). The Environmental Determinants of Diabetes in the Young (TEDDY) study (27) is exploring the role of putative environmental etiologies. Because causality of type 1 diabetes has not been conclusively demonstrated, environmental factors do not currently contribute to screening for risk, staging, or prevention of the disease.

The impact of HLA and non-HLA genetic risk is observed in relatives of individuals with type 1 diabetes, who have a 10-fold to more than 100-fold greater risk than the general population (Table 1). The cumulative risk of developing type 1 diabetes among
monozygotic twins is reported to be as high as 65–70% (28), with higher rates observed when the proband develops type 1 diabetes at an earlier age (29). A high risk is also observed in siblings of individuals with type 1 diabetes who are DR3-DQ2/DR4-DQ8 and have inherited both HLA haplotypes identical by descent with their proband sibling, with a risk as high as 80% for developing type 1 diabetes-associated autoimmunity by age 15 years (30). In siblings with shared DR3-DQ2/DR4-DQ8 HLA haplotypes, the age of onset of symptomatic type 1 diabetes in the proband is a prominent risk factor, with a 12-fold higher risk of developing symptomatic disease by age 15 years in the sibling if the proband develops the disease before age 10 years (31).

This increased risk in relatives of individuals with type 1 diabetes has been exploited in the research setting to identify at-risk individuals to better understand the natural history of type 1 diabetes and to conduct trials to prevent symptomatic disease, as exemplified by the Diabetes Prevention Trial–Type 1 (DPT-1) (4,32) and the National Institute of Diabetes and Digestive and Kidney Diseases–sponsored Type 1 Diabetes TrialNet studies (33). Approximately 15,000 children and young adults who are first- or second-degree relatives of individuals with type 1 diabetes are screened annually for the presence of islet autoantibodies through TrialNet (33). A recent position statement of the American Diabetes Association (ADA) recommended that at-risk relatives of individuals with type 1 diabetes be informed of the opportunity to have their relatives tested for type 1 diabetes risk in the setting of a clinical research study (34). Although screening more

Table 1—Type 1 diabetes risk stratification by family history and genetic susceptibility

| Population | Risk of type 1 diabetes (%) | Frequency in population (%) | Frequency in all type 1 diabetes (%) |
|------------|-----------------------------|----------------------------|------------------------------------|
| Low risk (<1%) |                             |                            |                                    |
| Newborns: European/U.S. population | 0.4–1          | 100                        | 100                                 |
| Newborns with HLA protective genotypes (124) | <0.05         | 75                         | 7.2                                 |
| FDR with HLA protective genotypes (124) | 0.3            | 0.3                        | <1                                  |
| FDR with low gene risk score* (HLA and non-HLA risk genes) (23) | <1            | 0.1                        | <1                                  |
| Intermediate risk (1–12%) |                             |                            |                                    |
| Newborns with HLA high-risk genotypes (37) | 4               | 4–5                       | 36                                  |
| Newborns with high gene risk score** (HLA and non-HLA risk genes) (23) | 12               | 1                          | 27                                  |
| Newborn first-degree relatives of people with type 1 diabetes | 5               | 0.5–1                     | 10                                  |
| High risk (12–25%) |                             |                            |                                    |
| FDR plus HLA high-risk genotypes (125) | 10–20          | 0.1                       | <5                                  |
| FDR plus high gene risk score*** (HLA and non-HLA risk genes) (23) | 40              | 0.1                       | <5                                  |
| Multiple affected FDRs (126) | 20–25          | <<0.1                    | <<5                                 |
| Very high risk (>25%) |                             |                            |                                    |
| Identical twin of a patient with type 1 diabetes (28,29) | 30–70         | <<0.1                    | <<5                                 |
| Multiple affected FDRs plus HLA risk genotypes (126) | 50               | <<0.1                    | <<5                                 |
| Sibling affected plus HLA risk genes, identical by descent (30) | 30–70         | <<0.1                    | <<5                                 |

FDR, newborn first-degree relatives of people with type 1 diabetes. HLA risk genotypes: HLA *DRB1* *03* and *04 and DQB1* *0302. HLA protective genotypes: HLA *DQB1* *0602, *0301, *0303, *0603,* and *0503. Genetic risk score derived from HLA plus nine single nucleotide polymorphisms from *PTPN22, INS, IL2RA, ERBB3, ORMDL3, BACH2, IL27, GLIS3,* and *RLNS* genes. *Threshold set to lower 10th centile of FDR; **threshold set to upper 90th centile of general population; ***threshold set to upper 90th centile of FDR.
than 150,000 individuals over the past decade by TrialNet represents a formidable accomplishment, screening of relatives leaves a large gap in identifying individuals at risk for developing type 1 diabetes because a family history of type 1 diabetes is present in only up to ~15% of cases of newly diagnosed type 1 diabetes (35,36).

On the basis of HLA genotype risk of type 1 diabetes, newborns and infants in the general population have also been screened for risk in the research setting and subsequently recruited into natural history studies. The TEDDY study screened newborns from the general population using four high-risk HLA genotypes (90% specificity, 69% sensitivity, and 22% positive predictive value) and newborns with first-degree relatives using 10 HLA genotypes (94% specificity, 50% sensitivity, and 4.8% positive predictive value), a strategy predicted to identify 50% of type 1 diabetes cases from the general population study and 70% of cases among relatives that occurred by age 15 years (37). It should be emphasized that the majority of HLA at-risk individuals never develop symptomatic type 1 diabetes and thus the positive predictive value of HLA is low, necessitating follow-up with additional biomarkers to detect risk of developing symptomatic disease, such as the presence of islet autoantibodies.

STAGE 1: AUTOIMMUNITY+/NORMOGLYCEMIA/ PRESYMPTOMATIC TYPE 1 DIABETES

Stage 1 is defined as the presence of two or more islet autoantibodies to insulin, GAD65, IA-2, and/or ZnT8. The mechanisms leading to β-cell autoimmune reactivity have not been completely elucidated. (Pro)insulin, GAD65, IA-2, and ZnT8 and their peptides have been identified as target antigens in type 1 diabetes (38,39). Although T lymphocytes are thought to be primarily responsible for β-cell destruction, they are rare in the circulating blood, and no standardized and validated human T-cell assays have been developed to screen for T-cell-mediated β-cell reactivity. However, islet autoantibodies are also generated and remain in the circulation and can be measured with standardized, sensitive, and high-throughput assays. Ongoing studies of T-lymphocyte phenotype, cytokine patterns of antigen-specific T cells, lymphocyte-mediated immunoregulation, and responses of effector T cells to immunoregulation of autoantibody-positive subjects prior to symptomatic disease should provide further insights into the role of T-cell responses and ultimately may provide useful biomarkers.

In Finnish and German at-risk children followed longitudinally from birth, islet autoantibodies were initially detected after 6 months of age and peaked between 9 and 24 months of age with a median age of detection of 15 months (40,41). In the TEDDY study of at-risk infants and children, the initial detection of islet autoantibodies occurred rarely prior to 6 months of age and peaked between 9 and 24 months of age (42). In most cases, autoantibodies to insulin developed earlier than autoantibodies to GAD65, whereas IA-2 and ZnT8 were rarely the first autoantibody to develop (9,40–44).

Progression from single to two or more autoantibodies occurs more commonly in children less than 5 years of age, usually occurs within 2 years of initial seroconversion, and is less frequent after 4 years of initial seroconversion (40–45).

Early autoantibody seroconversion is most common in children with the high-risk HLA DR3/4-DQ8 or DR4/4-DQ8/8 genotype (40–42), and the order of appearance of autoantibodies is related to HLA-DQ genotype. In the TEDDY study, HLA-DQ2/8, DQ8/8, and DQ4/8 children developed primarily insulin autoantibodies as the first autoantibody, whereas DQ2/2 children initially developed GAD65 autoantibodies (42). The associations between insulin autoantibodies and HLA-DQ8, but not DQ2, and between GAD65 autoantibodies and HLA-DQ2, but not DQ8, are also observed in new-onset type 1 diabetes (46–48). These findings suggest the possibility of a distinct etiopathogenesis related to HLA.

TrialNet autoantibody screening of relatives of individuals with type 1 diabetes has a yield of ~5% autoantibody positivity, and those with autoantibodies are further staged for risk with metabolic and genetic tests (33). For those subjects who are initially autoantibody negative, the rate of seroconversion is higher in relatives younger than age 10 years, with about 75% of seroconversions occurring by age 13 years (49,50).

The detection of two or more islet autoantibodies increases the rate of progression to symptomatic type 1 diabetes. In a study of 585 high-risk children with two or more islet autoantibodies enrolled in three prospective birth cohort studies (U.S. Diabetes Autoimmunity Study in the Young [DAISY], Finnish Diabetes Prediction and Prevention [DIPP] study, and German BABYDIAB and BABYDIET studies), symptomatic type 1 diabetes developed in 43.5%, 69.7%, and 84.2% at 5, 10, and 15 years of follow-up (Fig. 2) (7). Thus, the lifetime risk of developing symptomatic type 1 diabetes approaches 100% once two or more islet autoantibodies are detected in genetically at-risk children.

The number of detectable islet autoantibodies correlates with risk. In the high-risk birth cohort noted above, symptomatic disease occurred by 15 years after seroconversion in 12.7%, 61.6%, and 79.1% of children with a single, two, and three autoantibodies, respectively (7) (Fig. 3). In the TEDDY study, the 5-year risk of symptomatic diabetes was 11%, 36%, and 47%, respectively, in those with one, two, and three autoantibodies (9). Faster progression to symptomatic disease after seroconversion is also observed with younger age of seroconversion (<3 years) and HLA DR3-DQ2/DR4-DQ8 genotype and in female participants (7,9). In relatives of individuals with type 1 diabetes in DPT-1, the 5-year risk of developing symptomatic disease with multiple autoantibodies ranged from ~25% for two autoantibodies to 40% for three autoantibodies and 50% for four autoantibodies (Fig. 4) (8).

On the basis of these observations, universal childhood population-based screening for multiple autoantibodies was initiated in January 2015 in 200,000 healthy children at well-child visits at ages 3 and 4 years in Bavaria, Germany, in the Fr1da study (51). Multiple autoantibody-positive children will be offered the opportunity to enroll in an intervention clinical trial to arrest disease progression.

The rate of progression to symptomatic disease in the presence of two or more islet autoantibodies is associated not only with the number of
autoantibodies detected and the age of autoantibody seroconversion but also with the magnitude of the autoimmunity titer, affinity of the autoantibody, and the type of autoantibody (9,42,52–56). Higher titers of insulin and IA-2 autoantibodies are associated with earlier onset of symptomatic type 1 diabetes. The presence of IA-2 or ZnT8 autoantibodies is associated with faster progression to symptomatic disease compared with when both are absent. In first-degree relatives of individuals with type 1 diabetes, IA-2 and/or ZnT8 autoantibody seroconversion is associated with a 5-year progression rate to diabetes of 45% (57), and the presence of either of these autoantibodies is detected in 78% of progressors to symptomatic disease (58).

Thus, the presence of two or more autoantibodies is used as the major criterion for stage 1. The majority of individuals (85%) with a single autoantibody do not progress to overt symptomatic type 1 diabetes within 10 years. However, some single autoantibody subjects can progress, and progression appears to occur more frequently in children aged <5 years (44,45), if the single autoantibody is directed to IA-2 (7), or if the single autoantibody displays higher affinity (56,59,60). Assays that preferentially detect high-affinity autoantibodies or detect those single autoantibodies associated with progression to symptomatic type 1 diabetes are being investigated (56,59–62) and, if validated, may modify the criteria for the detection of two autoantibodies in stage 1 to include detection of single autoantibodies predictive of progression.

**STAGE 2: AUTOIMMUNITY+/DYSGLYCEMIA/PRESYMPTOMATIC TYPE 1 DIABETES**

Stage 2, like stage 1, includes individuals with islet autoantibodies but whose disease has now progressed to the development of glucose intolerance, or dysglycemia, that arises from loss of functional β-cell mass. Dysglycemia in this stage of type 1 diabetes has been defined in several studies by impaired fasting plasma glucose of ≥100 mg/dL (≥5.6 mmol/L) or ≥110 mg/dL (≥6.2 mmol/L), impaired glucose tolerance with 2-h plasma glucose with a 75-g oral glucose tolerance test (OGTT) of ≥140 mg/dL (≥7.8 mmol/L), high glucose levels at intermediate time points on OGTT (30, 60, 90 min levels of ≥200 mg/dL [≥11.1 mmol/L], and/or HbA1c ≥5.7% [≥39 mmol/mol]. At this stage of the disease, there is ~60% risk in 2 years and ~75% risk in 4–5 years of
developing symptomatic type 1 diabetes, with a positive predictive value of 96% within 5 years (Fig. 5) (10,63). It is not clear, however, whether the ADA or the American Association of Clinical Endocrinologists (AACE) diagnostic laboratory criteria, which were developed to diagnose prediabetes in the type 2 diabetes setting (64,65), are the optimal values for predicting rate of progression to onset of symptomatic type 1 diabetes, or stage 3 of type 1 diabetes. Metabolic testing, however, has been the key measurement of functional β-cell mass in this stage of the disease (66,67).

There is an accelerated decline in the first-phase insulin response on intravenous glucose tolerance tests during the progression to type 1 diabetes, which becomes especially marked between 1.5 and 0.5 years before diagnosis (68). A first-phase insulin response less than the first percentile is associated with a 50% risk of developing symptomatic type 1 diabetes within 1 year (69).

Individuals in this stage have, on average, a prolonged, gradual metabolic deterioration with the persistence of substantial β-cell function until at least 6 months before type 1 diabetes occurs (70). The 2-h OGTT glucose levels best predicted progression to disease in DPT-1 (71) but did not begin to change until ~0.8 years before diagnosis and then rose rapidly (72). In high-risk relatives of individuals with type 1 diabetes, β-cell glucose sensitivity as measured by the OGTT decreases up to 1.45 years prior to symptomatic disease and correlates with type 1 diabetes progression independent of sex, age, BMI, and clinical risk (72). Impaired β-cell glucose sensitivity is also prognostic for progression from prediabetes to type 2 diabetes (73,74). In contrast, baseline insulin sensitivity, fasting insulin secretion, and total postglucose insulin output were not predictive of progression (72). There can be transient reversion from a dysglycemic to a normal OGTT in this setting, but such does not alter the rate of progression to symptomatic disease in at-risk children (63,75).

A decrease in stimulated C-peptide lags behind changes in the OGTT. An accelerated decline in stimulated C-peptide levels is observed ~6 months prior to symptomatic type 1 diabetes, with a faster decline 3 months prior to the symptoms (76), while fasting C-peptide levels are maintained in the normal range during this period (70). At 4 years from the time of a 20% decrease in C-peptide from baseline, there is a 47% risk of symptomatic type 1 diabetes, with a positive predictive value of symptomatic type 1 diabetes within 5 years of 78% (10).

Increased insulin resistance or decreased insulin sensitivity can be observed in the later stages of progression to symptomatic type 1 diabetes and may contribute to β-cell dysfunction (75,77–79).

Although used as a diagnostic criterion for type 2 diabetes, an increased HbA1c level has variable performance as a marker for type 1 diabetes. In the prospective DPT-1, TEDDY, Trial to Reduce IDDM in the Genetically at Risk (TRIGR), and TrialNet Natural History studies, HbA1c ≥6.5% (≥48 mmol/mol) had very low sensitivity but high specificity for progression (80). However, increasing HbA1c at levels <6.5% (<48 mmol/mol) may be observed in the 12–18 months before symptomatic disease and occurs independent of abnormal random fasting glucose levels and the number of autoantibodies. Thus, increasing HbA1c may serve as a biomarker of type 1 diabetes progression (10,81,82). Analysis of TrialNet Natural History data showed that a 10% increase in HbA1c above baseline in subjects with multiple autoantibodies was associated with an 84% 3-year risk of developing either ADA diabetes diagnostic laboratory criteria or symptomatic type 1 diabetes, and a 20% increase in HbA1c was associated with a nearly 100% risk over 3–5 years, with a 5-year positive predictive value of 98% (10). In the Finnish HLA at-risk childhood cohort, a 10% increase in HbA1c

![Figure 4](https://care.diabetesjournals.org)

**Figure 4**—Probability of progression in islet autoantibody-positive relatives of individuals with type 1 diabetes stratified for number of autoantibodies (8).

![Figure 5](https://care.diabetesjournals.org)

**Figure 5**—Probability of progression from dysglycemia stage 2 in DPT-1. IGT, impaired glucose tolerance [unpublished data from DPT-1 (4,32)].
levels in samples taken 3–12 months apart increased risk 6-fold and predicted the diagnosis of clinical diabetes (hazard ratio 5.7), which had its onset with a median time of 1.1 years. In addition, two consecutive HbaA1c values ≥5.9% (≥41 mmol/mol) were associated with a 12-fold risk (hazard ratio 11.9) with a median time until diagnosis of 0.9 years (82).

At-risk children and adults who have been intensively followed in prospective natural history clinical research studies with monitoring for dysglycemia (i.e., OGTT, intravenous glucose tolerance test, HbaA1c) are frequently started on insulin replacement therapy in the absence of symptoms based on exhibiting ADA diagnostic criteria and, if the TEDDY study, 30% of children aged 14 years were presymptomatic at the time of diagnosis of type 1 diabetes, which over the long-term may make the disease easier to manage, decrease hypoglycemic episodes, delay the development of long-term complications, and decrease cost. Preservation of C-peptide secretion is linked to reduced risk of progression of retinopathy, nephropathy, and neuropathy and a lower risk of hypoglycemia (92,93). Moreover, intensive diabetes treatment begun after the diagnosis of symptomatic type 1 diabetes improves the likelihood of a honeymoon phase (94), helps patients to maintain higher C-peptide levels (92), and decreases mortality (95), suggesting that patients who are treated as early as possible will have improved long-term outcomes.

About one-half of diagnosed DPT-1 participants had HbaA1c levels within the normal range with an average HbaA1c value of 6.4% (46 mmol/mol) (86), a figure much less than the 10.9% (96 mmol/mol) average HbaA1c value in a cohort of children diagnosed in the community (83). A significant proportion of DPT-1 participants (35.4%) had normal fasting glucose levels at diagnosis, and nearly all (96.6%) had detectable C-peptide levels >0.2 ng/dL (86). DAISY children had lower HbaA1c levels for at least 1 month and lower insulin requirements for 12 months after the diagnosis compared with children diagnosed in the community (83), and children participating in the Diabetes Prediction in Skåne (DiPiS) longitudinal study had lower HbaA1c levels at 12 and 24 months after the diagnosis in the face of similar daily insulin dose requirements (96).

**CURRENT BENEFITS OF STAGING TYPE 1 DIABETES**

There are beneficial short-term clinical outcomes for subjects followed prospectively in natural history studies. In DAISY, a study of genetically at-risk children, only 3% of study participants were hospitalized at diagnosis compared with 44% of age- and sex-matched children diagnosed in the community (83). In the TEDDY study, 30% of children aged <5 years were presymptomatic at the time of diagnosis of type 1 diabetes based on ADA diagnostic criteria and, if symptomatic, were significantly less likely to experience DKA at onset than comparable populations (84). Similarly, in the German BABYDIAB and the Munich Family Study, children who were followed after screening positive for islet autoantibodies had a lower prevalence of DKA (85). A majority of DPT-1 study participants (63.3%) were diagnosed with type 1 diabetes based on laboratory metabolic parameters without symptoms, with only 3.67% developing DKA (86). In contrast, DKA at onset of type 1 diabetes was observed in ~30% of youth in the population-based SEARCH for Diabetes in Youth (SEARCH) study (87) and affected 46% of youth at diagnosis in Colorado in 2012, representing a 55% increase from 1998 to 2012 (88). DKA at onset of type 1 diabetes is associated with increased mortality and longer hospitalizations; is less likely to be associated with a partial remission, or “honeymoon phase”; and is more commonly associated with lower residual β-cell function, worse metabolic control, higher insulin requirements, and adverse short-term neurocognitive outcomes (85,89–91).

Children diagnosed through prospective natural history studies of type 1 diabetes often have better metabolic indicators both at and shortly after the diagnosis, which over the long-term may make the disease easier to manage, decrease hypoglycemic episodes, delay the development of long-term complications, and decrease cost. Preservation of C-peptide secretion is linked to reduced risk of progression of retinopathy, nephropathy, and neuropathy and a lower risk of hypoglycemia (92,93). Moreover, intensive diabetes treatment begun after the diagnosis of symptomatic type 1 diabetes improves the likelihood of a honeymoon phase (94), helps patients to maintain higher C-peptide levels (92), and decreases mortality (95), suggesting that patients who are treated as early as possible will have improved long-term outcomes.

**REFINEMENT OF STAGING**

Staging type 1 diabetes and predicting its progression will be refined during this decade. As described above, improved assays for detecting autoantibodies, and especially single, high-affinity autoantibodies, are being developed, and future efforts will need to focus on their clinical significance and standardization. Furthermore, in a small number of people who appear clinically to have type 1 diabetes at the time of clinical diagnosis, existing antibody measurements may fail to detect the presence of autoimmunity. Whether these individuals have an autoimmune process to an as-yet-unidentified antigen or another disease, such as monogenic diabetes, is unknown, and studies are ongoing to explore this. Efforts are under way to better predict the risk of development of autoimmunity and its earliest stages using metabolomics (101–105), microbiome metagenomics (106–110), and transcriptomics (111,112), among others. Decreased levels of phospholipids, especially choline-containing phospholipids, in umbilical cord blood have been detected in at-risk children who progress to symptomatic type 1 diabetes early in life (101–103) and, if validated, may provide informative markers for earlier staging. A type 1 interferon signature is detected in HLA genetically predisposed children prior to the development of autoantibodies (113,114) and may provide a novel
Diagnostic approaches for early risk detection. These approaches may ultimately help to define a new stage that occurs prior to the current stage 1.

New diagnostic approaches to refine staging are under development. A major limitation of detecting islet inflammation or insulitis associated with type 1 diabetes is the inability to image inflammation in the pancreas. Refined islet imaging approaches have demonstrated the ability to detect islet inflammation in new-onset type 1 diabetes (115) and will likely be applied to earlier stages of the disease. Analysis of ongoing β-cell destruction by detecting circulating demethylated insulin DNA is being investigated in both new-onset type 1 diabetes and the at-risk settings, and the assays are being refined and validated (116–120). There are also ongoing efforts to integrate and model diverse data (genetic, immunologic, metabolic, age, etc.) to develop composite predictive risk scores to better predict progression (121–123).

For broad application and acceptance, it will prove critical to have well-standardized validated biomarker assays. Long-term efforts will need to focus on working with regulatory authorities around biomarker qualification and adoption of surrogate biomarkers that can substitute for true clinical end points for clinical trials to arrest progression to symptomatic type 1 diabetes.

**CONCLUSIONS AND RECOMMENDATIONS**

Disease staging classification approaches have been used successfully for other disorders and have provided a framework for both diagnosis and therapeutic interventions. The type 1 diabetes staging classification recommendation presented herein captures the natural history and predictability of progression in at-risk individuals and provides a framework for research and development of preventive therapies and, ultimately, their adoption for clinical care.

At the present time, this classification system should be used for clinical research where it will aid in design of risk screening, clinical trial subject stratification, and design of natural history and intervention clinical trials, but risk screening and staging as outlined here are not recommended at this time for clinical practice in the absence of cost-effective screening, staging, and effective interventions that delay progression to symptomatic type 1 diabetes.

Human type 1 diabetes is a continuum that can be staged, starting with the detection of two or more islet autoantibodies (stage 1) and progressing at a variable rate to a second stage of glucose intolerance or dysglycemia (stage 2) before becoming clinically symptomatic (stage 3). The time of onset of symptomatic disease can be predicted based on stage-specific biomarkers. This classification system, which will be continuously refined with the development of novel stage-specific biomarkers, provides a new taxonomy of type 1 diabetes and a framework for clinical trial design, benefit/risk decisions around interventions, and, ultimately, the practice of precision medicine to prevent symptomatic type 1 diabetes.

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