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Utility of Diabetes-Associated Autoantibodies for Classification of New Onset Diabetes in Children and Adolescents

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Abstract

Objective—To determine whether measuring diabetes-associated autoantibodies (DAA) in pediatric new onset diabetes (NODM) can be restricted to patients with equivocal diabetes type.

Research Design and Methods—Retrospective analysis of all patients with NODM admitted to Boston Children's Hospital from 10/1/07–7/1/13 who had measurement of DAA (glutamic acid decarboxylase, insulin, IA-2). Data collection included initial diagnosis of diabetes type before DAA results and at follow up. We used logistic regression to predict type 1 diabetes (T1D) and developed a clinical score to classify diabetes type.

Results—Of 1089 patients (45.1% female, 76.7% White, age 10.6 ± 4.5 years), initial diagnosis was 1021 (93.8%) T1D, 42 (3.9%) type 2 diabetes (T2D), and 26 (2.4%) other. Of 993 patients with clinical T1D, 78 (7.9%) were DAA–, and of 42 patients with clinical T2D, 12 (28.6%) were DAA+. Type of diabetes was reclassified at follow up in less than 6% of patients. Data from a subset of 736 patients were used to develop a scoring system to predict T1D. Using weight z-score, age and race, the scoring system had 91.7% sensitivity, 82% specificity and a positive predictive value of 98.6%, and suggested DAA measurement was unnecessary in 85.3% of patients. Findings were similar in a validation cohort of 234 patients.

Conclusions—Application of a simple scoring system may reduce to ~15% the number of DAA measurements needed to classify diabetes type, resulting in substantial cost savings. Clinical judgment should guide the decision to measure DAA.

Keywords

Insulin Antibody; ICA512 Autoantibody; GAD65 (217–236); Diabetes Mellitus; Classification

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CONFLICT OF INTEREST:

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INTRODUCTION

Diabetes is classified into four general categories: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus, and specific types of diabetes due to other causes (1). However, viewed from a pathophysiologic perspective, diabetes results from a spectrum of insulin deficiency and insulin resistance. In children and adolescents, insulin deficiency is usually attributed to autoimmune destruction of beta-cells; monogenic disorders affecting insulin secretion are uncommon causes of insulin deficiency (1,2). The utility of classifying diabetes type has been debated (3,4); however, it is undoubtedly important to characterize subjects for research studies, and in clinical practice classification influences management decisions.

In children and adolescents with NODM, the presentation, clinical phenotype and family history primarily inform the designation of diabetes type (5,6). However, clinical features of T1D and T2D have increasingly become less distinct, and monogenic forms of diabetes may be difficult to distinguish clinically from both T1D and T2D (7–9). The SEARCH for Diabetes in Youth study group based the etiological classification of diabetes type on determination of autoimmunity and insulin sensitivity, and suggested this strategy be used by researchers and clinicians for the etiologic classification of diabetes type (2). To more accurately characterize diabetes type, these investigators have developed and validated a formula using waist circumference, HbA1c and triglycerides to estimate insulin sensitivity (10). Others have proposed using a combination of autoimmune status and C-peptide levels as a proxy for beta cell function to define type of pediatric diabetes (11).

The most recent ISPAD guidelines state that DAA measurement “may assist in confirming diabetes type” (5), and the recommendation to measure DAA is restricted to children suspected of having T2D and to obese patients with a clinical picture suggestive of T1D (6). At many institutions pediatric endocrinologists routinely measure diabetes-associated autoantibodies (DAA) in all children with NODM at the time of diagnosis; however, this practice is controversial. There is not universal agreement regarding whether DAA should be measured in all patients with NODM, regardless of clinical presentation, or, alternatively, whether DAA measurement should be performed in selected patients in whom the type of diabetes is uncertain.

The main objective of this study was to evaluate the usefulness of a DAA panel in clinical practice. Specifically, we aimed to determine the number of patients whose diabetes type was reclassified after obtaining the results of the DAA panel, and to describe their clinical characteristics. We hypothesized that measurement of the DAA panel can be omitted in the majority of patients with a classic clinical presentation of T1D, and can be restricted to patients suspected of having either T2D or an equivocal diabetes type. We also aimed to develop and test the utility of a clinical scoring system to assist in the selection of patients for whom DAA measurement can be omitted.

RESEARCH DESIGN AND METHODS

Study Design and Study Population

This was a cross-sectional retrospective study of all patients with NODM presenting to Boston Children's Hospital (BCH) between October 1, 2007 and July 1, 2013. Patients were identified using BCH's Diabetes Inpatient Quality Improvement Database, which contains all patients with newly diagnosed diabetes mellitus, including their presumed diabetes type assigned by the inpatient diabetes care team before obtaining the results of the DAA panel. Patients met inclusion criteria if they had NODM and had DAA measured within 5 days of initial diagnosis. Exclusion criteria were a previous diagnosis of diabetes mellitus and neonatal diabetes. NODM was defined as random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with classic symptoms of diabetes mellitus (polyuria, polydipsia, weight loss) or a fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) (12). Diabetic ketoacidosis (DKA) was defined as venous pH < 7.3 . The study was approved by the Institutional Review Board at BCH.

Data Collection

We used Childrens 360, a data extraction tool linked to the electronic medical record, to obtain patient data. We collected information on age at diagnosis, race, anthropometric measures, and diabetes type as described above. Diabetes types were designated as T1D, T2D or other. For patients whose height was not recorded at diagnosis, outpatient visit heights closest to and within 60 days of the date of diagnosis were extracted to calculate the patient's body mass index (BMI) at diagnosis. We collected laboratory data including concentrations of plasma glucose, serum electrolytes, serum and/or urine ketones, hemoglobin A1c (HbA1c), venous blood gas (VBG), and DAA, which included autoantibodies to glutamic acid decarboxylase (GAD), insulin (IAA), and insulinoma-associated antigen-2 (IA-2).

Outcomes

Our main outcome was the proportion of patients in whom the DAA status changed the diabetes type at the time of diagnosis (hereafter referred to as initial diagnosis). Our secondary outcome was the performance of a clinical scoring system to identify those patients for whom the measurement of DAA can be omitted with minimal likelihood of an incorrect diagnosis.

Diabetes Group Definitions

Patients were classified into six groups based on their initial diagnosis and DAA status: T1D/DAA+, T1D/DAA-, T2D/DAA+, T2D/DAA-, other type/DAA+ and other type/DAA-. We assumed that T1D/DAA+ patients had autoimmune T1D and that T2D/DAA- patients had classic T2D. For all other groups, the first author carefully reviewed the clinic notes after diagnosis to determine the final assessment of diabetes type by the patient's pediatric endocrinologist (hereafter referred to as final diagnosis).

A final diagnosis of T1D was defined as either T1D/DAA+ or any initial diagnosis (T1D, T2D or other type) with follow-up assignment of T1D. Similarly, a final diagnosis of T2D

was either T2D/DAA– or any initial diagnosis (T1D, T2D or other type) with assignment of T2D at follow-up. For patients whose physician’s records documented uncertainty in the assignment of diabetes type (variously referred to as hybrid, type 1.5, type 3, double diabetes, mixed type, etc.), final diagnosis was designated as equivocal. All other types of diabetes distinct from T1D and T2D, such as iatrogenic, medication-induced, and monogenic diabetes, were designated as other.

Laboratory Analysis

Serum bicarbonate (HCO_3) concentration was measured using quantitative enzyme-based determination on the Roche/Hitachi cobas c systems platform (Roche Diagnostics, Indianapolis, IN). The VBG, plasma glucose and serum electrolytes were determined using the Radiometer ABL 825 instrument (Radiometer, Cleveland, OH). Urine ketone concentrations were measured using Acetest tablets (Bayer Healthcare, Whippany, NJ). Hemoglobin A1c (HbA1c) was measured by immunoassay using the Roche Integra 800 platform (Roche Diagnostics, Indianapolis, IN). GAD was measured by quantitative ELISA, IA-2 and IAA by quantitative radioimmunoassay (all at ARUP, Salt Lake City, UT, USA). Before January 1, 2009, IAA was measured in the Clinical Immunology Laboratory at the Joslin Diabetes Center using a competitive insulin antibody assay (13); GAD and IA2 were measured using quantitative radioimmunoassay (14).

Statistical Analysis

We used mean and standard deviation or median and interquartile range, as appropriate, for continuous variables and proportions for categorical variables to describe patient characteristics. Analyses of continuous data were performed with Student’s t-test and Wilcoxon rank sum test for normally and non-normally distributed data, respectively. Chi square test was used to compare categorical variables. Patients (n=32) were excluded from the primary analysis if no data for a final diagnosis of diabetes type were available.

For the development of the DAA clinical scoring system, patients were divided into a study cohort (January 1, 2009 – July 1, 2013) and a validation cohort (October 1, 2007 – December 31, 2008). The study cohort was used to build a logistic regression model to predict a final diagnosis of T1D. We first performed a univariate screen to assess the variables age, race (White vs. other), weight z-score, BMI z-score, DKA status, ketonuria, pH, serum HCO_3 concentration, plasma glucose concentration, and anion gap as predictors of T1D. We then used forward selection in a multivariable model to identify variables that remained predictors of T1D with a significance level of at least 0.1. C-statistics and receiver operating characteristics (ROC) were used to evaluate models including all significant predictors against simplified models including only a subset of significant clinical predictors. An area under the curve (AUC) >0.90 was defined *a priori* as the minimum requirement for the final model. Beta estimates of the selected predictors of T1D were used to weigh their importance and assign, accordingly, points for the scoring system. The ROC curve was used to determine a cut-off for classifying a patient as likely to have T1D and, therefore, not requiring DAA measurement. Results of each ROC curve were presented as mean AUC with 95% CI.

Performance of the scoring system was assessed by separately calculating sensitivity, specificity and positive predictive value in the study cohort and in the validation cohort.

For all analyses, p-value <0.05 was considered significant. Analyses were performed using SAS Software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

The cohort consisted of 1263 patients, of whom 1089 (86.2%) met eligibility criteria. The initial diagnosis was T1D in 1021 (93.8%), T2D in 42 (3.9%) and other type of diabetes in 26 (2.4%) patients. Baseline characteristics of patients are shown in Table 1. Patients with an initial diagnosis of T1D were more likely to be White, younger, have lower weight z-score and BMI z-score, ketonuria, and present with DKA. Of all eligible patients, 86.5% were positive for one or more DAA. The majority of patients tested positive for IA-2 (69.0%) and GAD (69.2%); less than half (40.6%) were IAA positive. Results of DAA status by initial diabetes type assigned at diagnosis are shown in Table 2.

Final Diagnosis

Data to assign a final diagnosis of diabetes type were available for 1057 patients (Table 3). Median time from initial diagnosis to most recent follow up assessment was 31 months (IQR 19, 47). Sixty patients (5.7%) had a change in their diagnosis following DAA panel results. Of 993 subjects who received an initial diagnosis of T1D, 78 (7.9%) had a negative DAA panel. Of these, the majority (66.7%) retained the diagnosis of T1D, whereas 26 (33.3%) received a different final diagnosis, including T2D (n=8), equivocal type (n=12), monogenic diabetes (n=3), diabetes related to propionic acidemia (n=1), abnormal insulin secretion related to Alagille syndrome (n=1), and steroid-induced diabetes (n=1). Of the 42 patients with an initial diagnosis of T2D, 30 (71.4%) and 6 (14.3%), retained a final diagnosis of DAA- and DAA+ T2D, respectively; whereas, in 6 (14.3%) patients the final diagnosis was changed to DAA+ T1D. Of the 22 patients who had an initial diagnosis of other type of diabetes, 13 (59.1%) received a final diagnosis of DAA+ T1D. All other patients were DAA - and were assigned a final diagnosis of equivocal type (n=3), T2D (n=3), monogenic diabetes (n=1), steroid-induced diabetes (n=1) and diabetes associated with cancer therapy (high dose dexamethasone, L-asparaginase, total body irradiation) (n=1).

Development of DAA Clinical Scoring System

The scoring system was developed based on the data from 809 patients in the study cohort (Figure 1). The univariate screen revealed age, weight z-score, BMI z-score, race, ketonuria, serum HCO₃ concentration, plasma glucose and BUN concentrations, BUN/creatinine ratio and anion gap as significant predictors of T1D. Given expected collinearity of BMI z-score and weight z-score, only the latter was introduced into the multivariable selection process. Age, weight z-score, race and ketonuria remained significant in the multivariable model. Comparison of a model including all four variables vs. only including the three variables age, weight z-score and race, revealed minimally different ROC characteristics with a small reduction in AUC (0.94 [95% CI 0.90–0.97] vs. 0.92 [95% CI 0.87–0.96]). Therefore, for

ease of implementation, the three-variable model was selected (Figure 2 A). Points for each of the 3 variables were assigned as shown in Table 4. Based on the ROC characteristics of the total score as a predictor of T1D, a cut-off of less than 3 points was chosen to predict T1D (Figure 2 B). Conversely, a score of 3 or more suggests obtaining a DAA panel to definitively determine the diabetes type.

Evaluation of DAA Clinical Scoring System

The scoring system was evaluated in 736 study cohort patients for whom weight z-score, race and age data were available. A total of 13.5 % (99 of 736 patients) received a score that recommended a DAA panel (Table 5). The scoring system had a sensitivity of 91.5%, specificity of 82% and PPV of 98.6% to predict T1D.

Of 248 patients in the validation cohort, 234 had no missing data for the variables weight z-score, race and age. Patients in the validation cohort had, on average, a 0.4% (4 mmol/mol) lower HbA1c level at diagnosis (10.9 ± 2.0 % [95 ± 22 mmol/mol] vs. 11.3 ± 2.3 % [99 ± 25 mmol/mol], $p = 0.01$). They were more likely than patients in the study cohort to be IAA positive (71.3% vs. 33.8%, $p < 0.0001$) and had a lower likelihood of being GAD positive (53.3% vs. 78.0%, $p < 0.0001$). However, there was no difference in the percentage of patients who had a positive DAA panel (91.1% vs. 88.2%, $p = 0.14$). The scoring system recommended a DAA panel in 10.7% (Table 5) and had a sensitivity of 93.3%, specificity of 90.9% and PPV of 99.5% in the validation cohort.

CONCLUSIONS

These results provide compelling evidence that in a predominantly White population, a clinical diagnosis of diabetes type could be made correctly in a majority of patients with NODM without measuring DAA. A different diabetes type was assigned after obtaining the results of a DAA panel in only a small number of patients. Further, although newer methods for measurement of multiple DAA are becoming more cost effective (15), we showed that a simple clinical scoring system has high sensitivity and specificity to identify patients with classic T1D, thereby limiting the need to measure DAA to only about 10 to 15% of patients.

In our large population of pediatric and young adult patients between 6 months and 25 years of age with NODM, we found that less than 6% of patients were reclassified by their physicians after the results of the DAA panel were available. Slightly higher rates of reclassification (based on C-peptide levels, DAA results, or clinical course) have been described in previous studies. For example, in a group of ethnically diverse patients, Lipton et al. reported that diabetes type was reclassified in 19.8% (22/111) patients over an average of 7.8 years of follow-up (16). In a cohort of 580 German and Austrian patients with T2D, 10.3% were reclassified, on average 2.4 years, after follow up (17). Rates of reclassification might be expected to be higher in ethnically diverse populations with more T2D. In our relatively small subset of 42 patients with an initial diagnosis of T2D, only 6 (14.3%) were reclassified as T1D. However, 12 (28.6%) could be classified as T1D based on their positive DAA status; alternatively, they may be classified as having a hybrid form of diabetes, referred to variably as type 1.5 or double diabetes (18–22).

Consistent with other reports (23,24), based on the measurements of insulin, GAD and IA-2 antibodies, 86.5% of our total population and 89.6% of patients with a clinical diagnosis of T1D were DAA+. Our scoring system showed high sensitivity and specificity to identify children with a final diagnosis of T1D. This is not surprising given that all three predictors used are strongly associated with lower fasting C-peptide levels at diagnosis (25), a strong predictor of beta-cell function decline (26), which occurs most rapidly in youth with autoimmune T1D (25).

The aim of our scoring system was to identify patients with the highest likelihood of having a diabetes type other than classic T1D and for whom DAA testing should be recommended. This strategy is consistent with the most recent ISPAD guidelines (5). Owing to the increased prevalence of overweight and obesity in youth in the general population, clinical features of T1D and T2D have, increasingly, become less distinct (27). Studies suggest approximately 10% to 30% of youth diagnosed clinically with T2D are DAA+ (18–20); these individuals have rates of beta cell failure and insulin sensitivity similar to patients with T1D, again suggesting likely misclassification (19,20,28). Several studies, including the TODAY study, have shown significant clinical and biochemical differences between DAA+ and DAA– youth with clinical T2D; however, distinction between DAA+ and DAA– individuals was not possible based on clinical grounds alone (20,28–30). Dabelea et al. showed that the main predictor of beta-cell decline in all forms of diabetes, regardless of BMI status, is autoimmunity (25), and that an assessment of insulin sensitivity can help to better characterize diabetes type in youth (10). Our scoring system is consistent with the notion that recognizing autoimmunity is particularly important in overweight and obese youth because it may impact clinical management, including the decision to initiate insulin therapy. For example, the scoring system always recommends DAA measurement for any obese child with a BMI z-score >2, who is older than 10 years of age, regardless of race. The scoring system appropriately recommended DAA measurement in 37/39 patients (94.9%) with a score ≥3 in whom the final diagnosis was T2D.

Our data also suggest that clinicians need to maintain a high level of suspicion for monogenic diabetes in children with a clinical phenotype suggestive of T1D, especially when DAA are not routinely measured. It has been suggested that it may be advisable to store a frozen serum sample obtained at the time of presentation for determination of DAA at a later time, if MODY is later suspected. Patients with maturity onset diabetes of the young (MODY) may be the hardest to recognize (31). In our cohort, one patient with MODY3 and one with MODY4 had a score ≥3, prompting DAA measurement, whereas 2 other patients, ultimately identified with MODY on the basis of clinical features, had a score of <3. Patients may also have *de novo* mutations; therefore, a detailed family history as well as the patient's clinical course with persistent C-peptide production should raise the suspicion of monogenic diabetes and lead to further investigation (31).

Several limitations of this study merit comment. First, its retrospective nature did not allow for rigorous phenotyping of our patients. Further, details regarding the rationale for the clinician's initial and final diagnosis recorded in the medical record were limited, including the impact of the DAA results on the assigned final diagnosis. However, we believe that availability of these details and/or the potential for misclassification in the clinical

assignment of a final diagnosis is unlikely to have changed the primary findings. Second, we excluded patients who did not have a DAA panel measured within 5 days of diagnosis. However, our analysis comparing patients who did and did not have DAA measured revealed that the two groups did not differ significantly, except for a higher rate of severe DKA and higher frequency of serum electrolyte abnormalities in patients who did not have a DAA panel measured. Third, the DAA panel obtained at BCH included GAD, IA-2 and insulin antibodies, but not islet cell or zinc transporter 8 antibodies. Adding measurement of the latter antibody to the three autoantibody panel might have increased autoantibody positivity by to 2–3 percent (32,33) and, most likely, would have affected the number of children with DAA– T1D, a majority of whom are classified as T1D by the scoring system. Lastly, the racial/ethnic composition of our diabetes population differs from other regions of the United States (34) and elsewhere in the world. These results, therefore, may only be generalizable to populations with a similar, predominantly White racial/ethnic composition. In populations with even greater homogeneity, a scoring system that includes ketonuria may be considered. However, the performance of a prediction model for T1D that included weight z-score, age and race when restricting the analysis to White patients from both cohorts (n=802) was no different from the analysis of subjects of all races (n=970) (data not shown).

In summary, our study provides data regarding the utility of determining the DAA status in a large cohort of predominantly White pediatric patients with NODM. We conclude that a simple scoring system can be used to select patients who are most likely to benefit from DAA measurement. We believe that DAA determination can be restricted to a relatively small number of selected patients with NODM. Regardless of initial diabetes type classification, careful evaluation of the clinical phenotype at presentation and over time, together with family history of diabetes, is crucial in determining appropriate diabetes management. Further prospective studies should evaluate how clinical presentation and determination of autoantibody status impact clinical management, in particular, for overweight and obese youth with diabetes.

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ABBREVIATIONS

BMI	body mass index
DKA	diabetic ketoacidosis
GAD	glutamic acid decarboxylase
HbA1c	Hemoglobin A1c
IAA	insulin autoantibody

IA-2	insulinoma-associated antigen 2
MODY	maturity onset diabetes of the young
NODM	new onset diabetes
DAA	diabetes-associated autoantibodies
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
VBG	venous blood gas

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Figure 1.
Study Algorithm

Figure 2.

ROC curves of multivariable model and of scoring system to predict type 1 diabetes. Figures represent ROC curves of the multivariable model including age, weight z-score and race as predictor of T1D (panel A), and of the total assigned score as predictor of T1D (panel B).

Based on the ROC curve in panel B, sensitivity and specificity are maximized at 3 points. A cut-off of <3 predicts T1D. DAA measurement is suggested for individuals whose score is 3.

Table 1

Characteristics of Subjects

	All (N=1089)	Type 1 (n=1021)	Initial Diagnosis Type 2 (n=42)	Other (n=26)	p-value*
Age (y)	10.6 ± 4.5	10.3 ± 4.4	15.3 ± 2.8	13.1 ± 3.5	<0.0001
Sex (% Female)	494 (45.4)	467 (45.8)	18 (42.9)	9 (34.6)	0.71
Weight z-score	0.20 ± 1.27	0.08 ± 1.18	2.52 ± 0.81	1.37 ± 1.42	<0.0001
BMI z-score	-0.03 ± 1.55	-0.16 ± 1.48	2.34 ± 0.72	1.17 ± 1.30	<0.0001
Race (%)					<0.0001
White	76.7	79.0	28.6	61.5	
Asian	1.4	1.4	0	3.9	
Black	6.3	4.7	35.7	23.1	
Other	8.8	8.1	26.2	7.7	
Missing	6.8	6.8	9.5	3.9	
HbA1c (%) (mmol/mol)	11.2 ± 2.3 (99 ± 25)	11.3 ± 2.2 (100 ± 24)	10.7 ± 2.8 (93 ± 30)	10.6 ± 2.2 (92 ± 24)	0.14
Ketoneuria (%)	77.9	79.8	46.3	60.0	<0.0001
DKA (%)	21.8	22.3	7.9	22.7	0.03
Severe †	3.6	3.7	2.6	4.6	0.74
pH‡	7.36 (7.31, 7.39)	7.36 (7.31, 7.39)	7.37 (7.35, 7.38)	7.36 (7.33, 7.38)	0.07
Serum Bicarbonate (mmol/L) ‡	21 (17, 24)	21 (16, 24)	22 (20, 24)	21 (18, 25)	0.01
Glucose (mg/dL) (mmol/L)	409 ± 178 (22.7 ± 9.9)	414 ± 176 (23.0 ± 9.8)	351 ± 198 (19.5 ± 11.0)	305 ± 142 (16.9 ± 7.9)	0.03
BUN (mg/dL) (mmol/L)	14 ± 6 (5.0 ± 2.1)	15 ± 6 (5.4 ± 2.1)	11 ± 5 (3.9 ± 1.8)	12 ± 4 (4.3 ± 1.4)	0.0004
Creatinine (mg/dL) (mmol/L)	0.47 ± 0.19 (41.6 ± 16.8)	0.46 ± 0.19 (40.7 ± 16.8)	0.59 ± 0.17 (52.2 ± 15.0)	0.56 ± 0.20 (49.5 ± 17.7)	<0.0001
BUN/Creatinine	34 ± 18	35 ± 18	20 ± 7	24 ± 9	<0.0001
Ratio					
Sodium (mmol/L)	132 ± 5	132 ± 5	134 ± 4	133 ± 3	0.08
Anion Gap	17 ± 6	18 ± 6	15 ± 6	16 ± 6	0.03

Data are presented as mean ± standard deviation, unless otherwise indicated.

* Comparison of type 1 vs. type 2 diabetes. Comparison for “other” diabetes type (n=26) not shown

‡ pH <7.1

(sign
median (interquartile range)
*)

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Table 2

DAA Positivity at Initial Diagnosis

	All N=1089 n (%)	Initial Diagnosis [*]			p-value [*]
		Type 1 n=1021 n (%)	Type 2 n=42 n (%)	Other n=26 n (%)	
DAA+	943 (86.5)	915 (89.6)	12 (28.6)	16 (61.5)	<0.0001
1 antibody+	217 (19.9)	203 (19.9)	8 (19.0)	6 (23.1)	
2 antibodies+	449 (41.2)	443 (43.4)	1 (2.4)	5 (19.2)	
3 antibodies+	277 (25.4)	269 (26.3)	3 (7.1)	5 (19.2)	
GAD+	751 [†] (69.0)	734 (71.9)	7 (16.7)	10 (38.5)	<0.0001
IA-2+	753 [‡] (69.2)	732 (71.7)	8 (19.0)	13 (50.0)	<0.0001
IAA+	442 [§] (40.6)	430 (42.1)	4 (9.5)	8 (30.8)	<0.0001

^{*} Comparison of type 1 vs. type 2 diabetes. Comparison for "other" diabetes type (n=26) not shown

[†] N missing = 21

[‡] N missing = 19

[§] N missing = 20

Table 3

Categorization of Subjects by Initial Diagnosis and Final Diagnosis

Initial Diagnosis/DAA status	Final Diagnosis			
	Type 1 (n=986)	Type 2 (n=47)	Equivocal (n=15)	Other (n=9)
Type 1 Diabetes				
DAA+	915 (86.6)	0	0	0
DAA–	52 (4.8)	8 (0.8)	12 (1.1)	6 (0.6)
Type 2 Diabetes				
DAA+	6 (0.6)	6 (0.6)	0	0
DAA–	0	30 (2.8)	0	0
Other				
DAA+	13 (1.2)	0	0	0
DAA–	0	3 (0.3)	3 (0.3)	3 (0.3)

Numbers in parentheses refer to the percentage of the total population (n=1057; 32 missing due to lack of follow up).

Table 4**DAA Clinical Scoring System**

Variable	Points	Beta Estimate (SE)
Weight Z-score		1.34 (0.19)
<1	0	
1–2	1	
>2	2	
Age		0.31 (0.06)
<10	0	
10–15	1	
>15	2	
Race		0.58 (0.15)
White	0	
Other	1	
TOTAL SCORE	If < 3 → assume type 1 diabetes	
	If ≥ 3 → obtain DAA panel	

Variables included in the scoring system, their categorization, and points assigned for each subcategory are shown. Beta estimates are shown for each variable and indicate the weight of one measurement unit of this variable in relation to the other two.

Table 5

Performance of Scoring System using Weight z-score, Age and Race

Score	Final Diagnosis			
	Type 1	Type 2	Equivocal	Other
Study cohort (n=736)	n=686	n=30	n=13	n=7
Score <3	628	2	4	3
<i>Likely Type 1, omit DAA</i>	(85.3)	(0.3)	(0.5)	(0.4)
Score 3	58	28	9	4
<i>Type 2 or other, obtain DAA</i>	(7.9)	(3.8)	(1.2)	(0.5)
Validation cohort (n=234)	n=223	n=9	n=0	n=2
Score <3	208	0	0	1
<i>Likely Type 1, omit DAA</i>	(88.9)	0	0	(0.4)
Score 3	15	9	0	1
<i>Type 2 or other, obtain DAA</i>	(6.4)	(3.9)	0	(0.4)

Numbers in parentheses represent percentages of all patients in their respective cohort (study or validation cohort).