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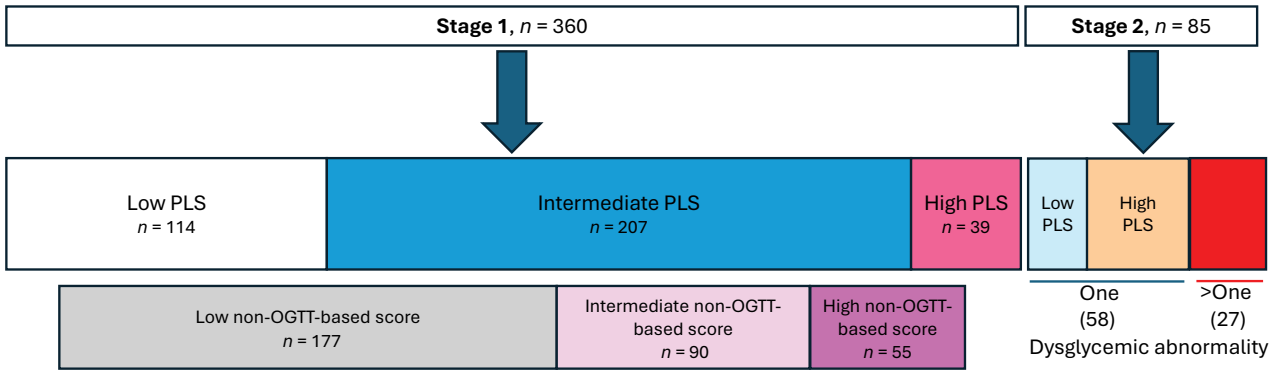

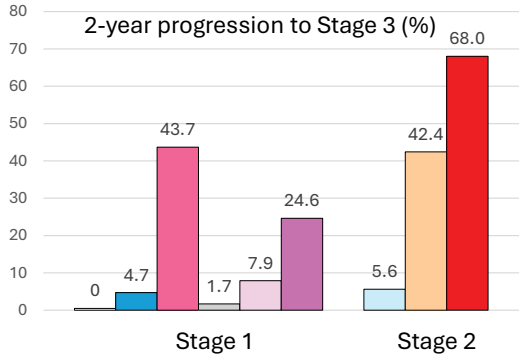

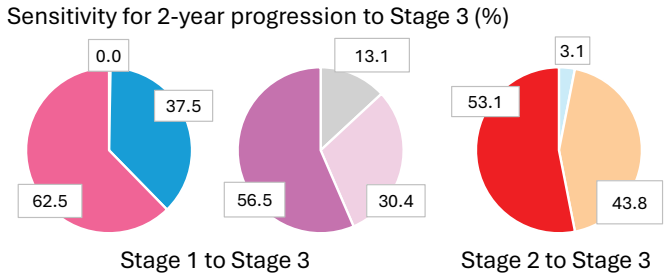

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To better stratify rates of progression from stage 1 or 2 to clinical stage 3 type 1 diabetes.
- **What are the specific questions we wanted to answer?**
  How effective is the progression likelihood score (PLS) in children classified as stage 1 or stage 2 according to current American Diabetes Association criteria? Can a PLS without the need for an oral glucose tolerance test stratify early risk for stage 3?
- **What did we find?**
  The PLS stratified the 2-year risk for stage 3 from 0 to 43.7% in children with stage 1 and was also effective in children with stage 2. A score without oral glucose tolerance test could also stratify risk.
- **What are the implications of our findings?**
  The PLS can help guide monitoring, counseling, and selection of participants for clinical trials.

Stratifying the Rate of Disease Progression by Progression Likelihood Scores in Children and Adolescents With Stage 1 and Stage 2 Type 1 Diabetes in Germany

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OBJECTIVE

To stratify the progression rate to clinical stage 3 type 1 diabetes in children with early-stage disease.

RESEARCH DESIGN AND METHODS

The Fr1da study tested 211,464 children aged 1.75–10 years for islet autoantibodies. Children with early-stage type 1 diabetes were classified as stage 1 or stage 2 by oral glucose tolerance test (OGTT) and hemoglobin A_{1c} (HbA_{1c}) using current American Diabetes Association criteria and were followed 3–6 months. We applied our previously developed progression likelihood score (PLS), a composite of HbA_{1c}, 90-min OGTT glucose, and islet antigen 2 antibodies (IA-2A) titer, and developed a non–OGTT-based score using multivariable Cox proportional hazards models to stratify progression rates to stage 3.

RESULTS

Of 485 children who participated in staging, 360 (74.2%) were diagnosed with stage 1. Of these, stage 3 developed in 105 (median follow-up 3.3 years). PLS stratified the 2-year risk for stage 3 from 43.7% (95% CI 24.3–58.1) in children with high PLS to 4.7% (1.7–7.7) and 0% in those with intermediate or low PLS. Adding the variable obesity improved the existing model. In children with stage 2 with a single dysglycemic abnormality, PLS could stratify 2-year risk for stage 3 from 42.4% (95% CI 22.8–57.0) to 5.6% (0.0–15.6). A non–OGTT-based score based on IA-2A titer categories, HbA_{1c}, obesity, and autoantibody positivity for IA-2 juxtamembrane epitopes could identify individuals with low (1.7%) and moderate (24.6%) 2-year risk.

CONCLUSIONS

The PLS and a novel non–OGTT-based score can stratify the short- to medium-term progression rates to stage 3 and should be considered for guiding monitoring practices and clinical trial eligibility.

The identification of individuals in the early, presymptomatic stages of type 1 diabetes is rapidly expanding (1–3). Early-stage type 1 diabetes is characterized by the

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presence of two or more islet autoantibodies and is further classified into stage 1 (normoglycemia) and stage 2 (dysglycemia) (4,5). Staging provides important estimates of the risk and rate of progression to clinical stage 3 type 1 diabetes (6,7). These risk estimates are reflected in monitoring guidelines to assess metabolic health (5) and in eligibility criteria for trials that assess the efficacy and safety of disease-modifying therapies.

Most individuals with early-stage type 1 diabetes identified by population screening are classified as stage 1 (1,6). On average, people in stage 1 progress more slowly to clinical stage 3 diabetes than those in stage 2 (6,8). For many disease-modifying intervention trials, especially those where the intervention therapy is expected to have greatest effects close to the clinical onset of diabetes, individuals with a relatively fast rate of progression, such as those with stage 2, are often preferred. However, stage 2 is relatively infrequent in population-based screenings. At the same time, although staging provides estimates of average progression risk, there is substantial interindividual variability within each stage (8,9).

To address this, we had developed a progression-likelihood score (PLS), based on values of hemoglobin A_{1c} (HbA_{1c}), islet antigen 2 (IA-2) autoantibody titer, and the 90-min glucose value from an oral glucose tolerance test (OGTT), to stratify risk within stage 1 (6). The PLS identifies a subgroup within those with stage 1 type 1 diabetes who have a relatively rapid progression, as well as approximately one-third of individuals who show no progression over the first 2 years. Others have developed dynamic scores that provide a risk estimate using algorithms of a range of variables (10–12). These attempts at risk scores may help improve the management of early-stage type 1 diabetes by enabling more cost-effective, risk-adapted follow-up strategies and potentially identify subgroups suitable for intervention therapies.

The PLS is practical since few measurements are required. However, dysglycemia definitions used to classify stage 1 and 2 continue to evolve, influencing estimates of disease progression. Earlier definitions of stage 2 required confirmed abnormalities in the OGTT, without incorporating HbA_{1c} (8,13). Current American Diabetes Association (ADA) criteria have aligned the definition of dysglycemia to that used for preclinical type 2 diabetes (4), which allows for a stage 2 classification based on a single unconfirmed glycemic abnormality, including HbA_{1c} or fasting glucose values down to 100 mg/dL. As a result, individuals previously classified as stage 1 may now fall under stage 2. Our PLS was developed using the earlier definition of stage 1, and how well the score performs under the current ADA staging criteria remains unclear. Furthermore, the PLS and similar tools rely on OGTT-derived measures, a procedure that is often poorly accepted by children and their families (14), limiting its practical use in large-scale screening or follow-up programs.

Here we examine *1*) the performance of the PLS in individuals with updated early-stage criteria and *2*) the potential of additional markers, such as islet autoantibody epitopes, to allow/permit risk stratification without OGTT. These analyses are conducted in an extended cohort of children diagnosed with early-stage type 1 diabetes in the Fr1da study as well as in an independent validation cohort from other Munich-based screening studies.

RESEARCH DESIGN AND METHODS

Study Population

Between February 2015 and June 2025, children in Bavaria, Germany, with no previous diagnosis of diabetes, were offered screening for islet autoantibodies by primary care pediatricians, as previously described (1,15,16). Children aged 1.75–5.99 years were eligible until March 2019, and children aged 1.75–10.99 years were eligible from April 2019 to June 2025. A total of 211,464 children with a median age of 4.3 years (interquartile range 3.2–5.7) participated in the screening. Families of children with more than one islet autoantibody (early-stage type 1 diabetes) were invited to participate in metabolic staging by OGTT and HbA_{1c} and in an educational program at a pediatric diabetes clinic close to their residence. Weight, height, and BMI were also assessed. Children were followed and monitored in 3- to 6-month intervals for progression to stage 3 type 1 diabetes; monitoring included HbA_{1c}, OGTT, home glucose measurements, and continuous glucose monitoring (17). The last follow-up date for this analysis was 26 June 2025. The study was approved by the Technical University Munich Institutional Review Board (Munich, Germany). Written informed consent was obtained from the children's parents or legal guardians. The study is registered at ClinicalTrials.gov (NCT04039945).

For validation, children from other Munich screening studies were used who fulfilled the Fr1da age criteria at screening and participated in staging and follow-up with 3- to 6-month OGTT and HbA_{1c} assessments. A total of 61 children with stage 1 type 1 diabetes were eligible (Table 1). These Munich screening studies were approved by the Technical University Munich Medical Faculty Ethics Committee, Munich, Germany (Nr 5668/13).

Stage Definition

Children who were classified as stage 1 or stage 2 type 1 diabetes were included in this analysis. Stage 1 was defined as normal glucose tolerance (fasting plasma glucose [FPG] of <5.6 mmol/L [100 mg/dL] and OGTT 2-h plasma glucose <7.8 mmol/L [140 mg/dL], and plasma glucose <11.1 mmol/L [200 mg/dL] at 30, 60, or 90 min in an OGTT), and HbA_{1c} <39 mmol/mol (5.7%). Stage 2 was defined as dysglycemia (FPG 5.6–6.9 mmol/L [100–125 mg/dL], 2-h plasma glucose 7.8–11.0 mmol/L [140–199 mg/dL], or 30-, 60-, or 90-min plasma glucose >11.1 mmol/L [200 mg/dL], or HbA_{1c} 5.7–6.4% or at least a 10% increase in HbA_{1c}. Stage 3 was defined by FPG ≥7.0 mmol/L (126 mg/dL) or a 2-h plasma glucose of ≥11.1 mmol/L (200 mg/dL) in an OGTT; or HbA_{1c} >48 mmol/mol (6.5%); or in children with classic symptoms of hyperglycemia, a random plasma glucose of >11.1 mmol/L (200 mg/dL). In the absence of unequivocal hyperglycemia, diagnosis required two abnormal results from different tests obtained at the same time (e.g., HbA_{1c} and FPG), or the same test at two different times (4,6).

Islet Autoantibody Determination

Insulin autoantibodies (IAA), GAD antibody (GADA), islet antigen 2 antibodies (IA-2A), zinc transporter-8 antibody (ZnT8A), and tetraspanin 7 antibody (TSpan7A), as well as epitope reactivity of IA-2A, were determined in serum samples collected at the staging visit. IAA were measured by a competitive radiobinding assay (RBA) with protein A/G immunoprecipitation and ^{125}I-labeled recombinant human insulin (18). GADA and IA-2A were measured according to the harmonized RBA protocol of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) using ^{35}*S*-methionine–labeled recombinant

Table 1—Children and adolescents participating in the Fr1da study or validation cohort study

	Stage 1 type 1 T1D				Stage 2 T1D	
	Fr1da cohort (*n* = 360)		Validation cohort (*n* = 61)		Fr1da cohort (*n* = 85)	
	n	*n* (%), or median (IQR)	*n*	*n* (%), or median (IQR)	*n*	*n* (%), or median (IQR)
Female sex	360	169 (46.9)	61	32 (52.5)	85	34 (40.0)
Age (years)	360	4.4 (3.3–5.7)	61	5.4 (3.5–7.7)	85	4.2 (2.9–5.5)
First-degree relative with T1D	360	56 (15.6)	61	36 (59.0)	85	15 (17.6)
IAA+	360	289 (80.3)	61	50 (82.0)	75	60 (80.0)
GADA+	360	322 (89.4)	61	55 (90.2)	74	61 (82.4)
IA-2A+	360	223 (61.9)	61	40 (65.6)	82	62 (75.6)
IA-2 JM epitope+	324	123 (40.0)		Not done		Not done
IA-2β epitope+	325	135 (41.5)		Not done		Not done
IA-2 PTP epitope+	325	169 (52.0)		Not done		Not done
ZnT8A+	360	242 (67.2)	61	44 (72.1)	74	59 (79.7)
HbA_{1c} (%)	360	5.2 (5.1–5.4)	61	5.3 (5.1–5.4)	85	5.6 (5.2–5.7)
Blood glucose (mg/dL)						
OGTT—0 min	359	80 (72–87)	61	80 (74–88)	83	85 (75–100)
OGTT—30 min	356	135 (115–155)	61	134 (106–159)	79	158 (129–193)
OGTT—60 min	359	118 (100–143)	61	111 (92–135)	80	158 (121–196)
OGTT—90 min	360	106 (90–121)	61	101 (89–124)	82	132 (106–174)
OGTT—120 min	358	100 (86–112)	61	97 (88–110)	81	125 (100–152)
BMI *z* score	352	0.2 (−0.5 to 0.9)	11	0.3 (−0.1 to 0.6)	79	0.1 (−0.6 to 0.8)

T1D, type 1 diabetes.

human N-terminal truncated GAD65 (amino acids 96–585) or IA-2 intracellular domain (amino acids 606–979), as previously described (19). ZnT8A was measured according to the NIDDK harmonized RBA protocol using ^{35}S-methionine–labeled recombinant human ZnT8 (amino acids 268–369) to separately detect autoantibodies against the arginine-325R and tryptophan-325 W ZnT8 variants (ZnT8RA and ZnT8WA, respectively), as previously described (20). Samples were classified as ZnT8A positive if they were positive for ZnT8RA and/or ZnT8WA. The assays had sensitivities and specificities of 52% and 100% for IAA, 82% and 99% for GADA, 78% and 100% for IA-2A, 66% and 100% for ZnT8RA, and 62% and 100% for ZnT8WA in the Islet Autoantibody Standardization Program (IASP) 2023 Workshop. TSpan7A was measured by a luciferase immunoprecipitation system assay, as previously described (21).

Children with sufficient remaining biosample material were measured for IA-2A epitope reactivities (*n* = 325) (Table 1). IA-2A epitope reactivities were determined by RBAs, as previously described (22). IA-2A binding was measured using ^{35}S-methionine–labeled IA-$2_{687–979}$ protein for antibodies to the protein tyrosine phosphatase (PTP)-like domain of IA-2 (IA-2 PTP), IA-$2_{389–779}$ protein for antibodies to the juxtamembrane region of IA-2 (IA-2 JM), and IA-$2\beta_{644–1015}$ protein for antibodies to the PTP-like domain of IA-2β (IA-2β PTP). The 99th percentile of control sera was used as the threshold for positivity for each antibody (3 units/mL for IA-2 PTP, 20 units/mL for IA-2 JM, and 3 units/mL for IA-2β PTP).

Progression Likelihood Score

The PLS is a composite score of HbA_{1c}, 90-min glucose during OGTT, and IA-2A titer, which is ordinally categorized into four categories: negative (0), >3–100 NIDDK units (1), 100–290 NIDDK units (2), and >290 NIDDK units (3). The score is calculated by the formula: $exp[(HbA_{1c}[\%] - 5.233) \times 1.125 + (OGTT90[mg/dL] - 107.6) \times 0.0195 + (IA\text{-}2Acat - 1.27) \times 0.662)]$. The 90th centile of the score in individuals with stage 1 type 1 diabetes identified by previous stage 1 criteria corresponded to a score of 4.0, and the 30th centile to 0.5 (6). For each participant, the PLS was calculated at first staging. For a sensitivity analysis that assessed the performance of the PLS in stratifying the progression rate from stage 2 to stage 3, the PLS was also calculated at the first occurrence of stage 2 in participants who developed stage 2 during follow-up.

Statistical Analysis

The progression to stage 3 type 1 diabetes was assessed using the Kaplan-Meier time-to-event method. Follow-up commenced from the calculation of the PLS. Children were censored when they developed stage 3 type 1 diabetes or reached the date of their final contact to ascertain diabetes status. Between-group comparisons in the Kaplan-Meier analyses were performed using the log-rank test. The Cox proportional hazards model was used to assess the association of factors with progression to stage 3. Thereby, sex, first-degree relative status, antibody/epitope positivity, and time of OGTT blood glucose peak were used as categorical variables, and OGTT (0-, 30-, 60-, 90-, and 120-min blood glucose), HbA_{1c}, BMI, and age as continuous variables. Prior to analysis, the BMI was transformed to a standardized BMI based on BMI-for-age *z* scores using World Health Organization reference values (23). Overweight status was defined as standardized BMI of 1 or 2 and obesity as BMI >2, according to World Health

Organization recommendations. For the Cox proportional hazards analysis, variables were first analyzed in univariable models. Significant variables were used in multivariate models to develop a non–OGGT-based progression score. The analysis and graphics were performed using R 4.4.1 software and the packages *survival* 3.4-0 and *survminer* 0.4.9 (24).

Data and Resource Availability

The deidentified individual participant data that underlie the results (text, tables, figures, and supplementary material) reported in this article can be shared between 9 and 36 months after publication of the article. Requests will be honored from researchers who provide a methodologically sound proposal and who complete a Data Use Agreement with Helmholtz Munich. Requests should be directed by e-mail to the corresponding author.

RESULTS

A total of 485 children participated in a staging and educational visit (Supplementary Fig. 1 and Table 1). Of those, 360 (74.2%) were diagnosed with stage 1, 85 (17.5%) with stage 2, 17 (3.5%) with stage 3, and 23 (4.7%) were not classified because OGTT or HbA_{1c} data were missing. Participants with stage 1 were followed for a median time of 3.3 years (interquartile range [IQR], 1.2–6.0). Of the 360 children with stage 1, 105 developed stage 3 at a median time of 4.0 years (IQR, 2.2–5.5) from staging, and 180 developed stage 2, including 73 who were identified with stage 2 prior to their progression to stage 3. Of the 85 with stage 2, 51 developed stage 3, and of the 23 not classified, 7 developed stage 2 and 9 developed stage 3.

Performance of Original PLS in Stage 1 Type 1 Diabetes

We applied our previously developed PLS and the previously established thresholds for high (>4.0, corresponding to the previously defined 90th percentile), intermediate (0.5–4.0), and low (<0.5, previously defined as the 30th percentile) values to the Fr1da and validation cohorts, using the current 2025 criteria for stage 1 diagnosis. Of the 360 children with stage 1 type 1 diabetes in the Fr1da cohort, the PLS was high in 39 (11%), intermediate in 207 (57%), and low in 114 (32%). The 2-year risk of progression to stage 3 was 43.7% (95% CI 24.3–58.1) in those with a high PLS, 4.7% (95% CI 1.7–7.7) in those with an intermediate PLS, and 0% in those with a low PLS ($P < 0.0001$) (Fig. 1*A* and Table 2). The 2-year progression rates in the validation cohort were 28.6% (95% CI 0.0–55.3), 5.1% (95% CI 0.0–11.8), and 0% in the high, intermediate, and low PLS categories, respectively ($P = 0.0001$) (Fig. 1*B*). The 3-year progression rates and median survival times are provided in Table 2. To further evaluate the predictive performance of the PLS, we conducted a receiver operating characteristic (ROC) curve analysis (Fig. 1*C*). The area under the curve (AUC) to identify those who progressed to stage 3 type 1 diabetes within 2 years ($n = 24$) was 0.852, indicating strong discrimination. A PLS >4.0 identified 15 of 24 children (62.5%) who progressed to stage 3 type 1 diabetes within 2 years and 21 of 45 children (46.7%) who progressed within 3 years.

The PLS is based on IA-2A measurements from a harmonized RBA (19). Since this is not universally available, we sought to validate the IA-2A component of the PLS using an electrochemiluminescence (ECL) assay that is in commercial development (25). The PLS groups <0.5, 0.5–4.0, and >4.0 were calculated using ECL IA-2A titer categories matched to the centiles for categories defined by the RBA result. Of the 360 children, 329 (91.6%) remained in the same PLS group. The three groups with the PLS defined using the ECL assay discriminated progression rates to stage 3, and there was no difference in the progression rates to stage 3 between the PLS derived from RBA or ECL IA-2A assays (Supplementary Fig. 2).

In summary, the previously defined PLS categories were able to discriminate rapid and slower progressors to stage 3 type 1 diabetes also in the extended Fr1da cohort using the updated current stage 1 ADA criteria.

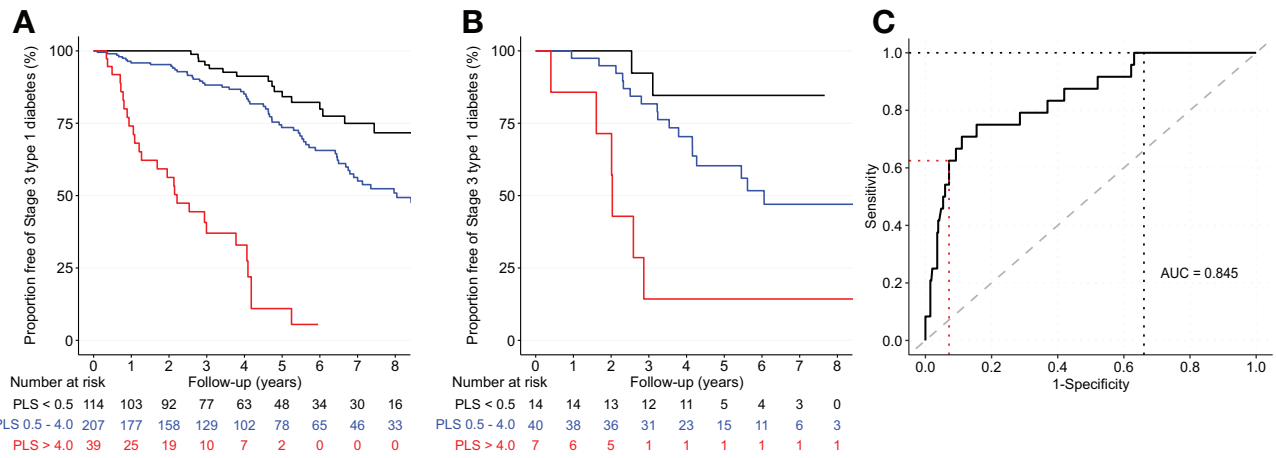

Figure 1—Stratification of progression from stage 1 to stage 3 type 1 diabetes by the original PLS. Kaplan-Meier survival curves for progression to stage 3 type 1 diabetes in children initially diagnosed with stage 1 type 1 diabetes in the Fr1da cohort (*A*) and the validation cohort (*B*). Children were categorized using previously defined PLS thresholds as <0.5 (low), 0.5–4.0 (intermediate), and >4.0 (high). Progression differed significantly among categories in both the Fr1da cohort ($P < 0.0001$) and the validation cohort ($P = 0.0001$). The numbers underneath the *x*-axis indicate the number remaining at each year of follow-up. *C*: ROC curve for the ability of the PLS to discriminate the 24 Fr1da cohort children with stage 1 who developed stage 3 type 1 diabetes within 2 years of follow-up (sensitivity) from the 269 who were followed for at least 2 years without developing stage 3 (1−Specificity). The vertical/horizontal dashed lines show the performance at the PLS thresholds of 0.5 (black) and 4 (red). The diagonal dashed line represents no discrimination. The AUC is 0.845.

Table 2—Risk of progression at 2 and 3 years to stage 3 type 1 diabetes from stage 1 and stage 2 and median survival

Stage/score	*n*	2-year progression rate to stage 3 T1D, % (95% CI)	3-year progression rate to stage 3 T1D, % (95% CI)	Median survival, years (95% CI)
Stage 1 T1D: Original PLS				
PLS >4.0	39	43.7 (24.3–58.1)	63.0 (41.7–76.5)	2.2 (1.3–4.1)
PLS ≤4.0 and >0.5	207	4.7 (1.7–7.7)	11.8 (6.8–16.6)	8.0 (6.8–>8.0)
PLS ≤0.5	114	0.0	4.9 (0.1–9.4)	>8.0
Stage 1 T1D: Non–OGTT-based progression score				
Score >3.0	55	24.6 (13.0–36.2)	37.7 (24.2–41.2)	4.1 (3.4–7.0)
Score ≥1.25 and ≤3.0	90	7.9 (2.4–13.4)	17.9 (9.7–26.1)	7.4 (5.3–>8.0)
Score <1.25	177	1.7 (0.0–3.7)	6.8 (2.7–10.9)	>8.0
Stage 2 T1D: Original PLS				
≥2 abnormalities	27	68.0 (42.4–82.2)	76.0 (45.7–89.4)	1.1 (0.6–NR)
1 abnormality	58	30.2 (16.6–41.6)	36.7 (21.9–48.7)	3.8 (3.1–7.3)
PLS >1.6	35*	42.4 (22.8–57.0)	48.8 (28.4–63.4)	3.1 (1.3–6.4)
PLS ≤1.6	20*	5.6 (0.0–15.6)	12.3 (0.0–27.0)	7.3 (6.0–NR)

Results are stratified by the PLS (6) and a new non–OGTT-based progression score, calculated from Kaplan-Meier analyses. NR, not reached; T1D, type 1 diabetes. *Three had missing data for PLS relevant variables.

Additional Variables Associated with Progression to Stage 3 Type 1 Diabetes

To explore possible improvement of the progression score, we investigated the association between additional variables and the rate of progression to stage 3 diabetes (Supplementary Fig. 3). In addition to the parameters used in the PLS, the following variables were significantly associated with increased rates of progression to stage 3 in the univariable analysis: 60-min OGTT (hazard ratio [HR] 1.15, 95% CI 1.06–1.24 for a 10-unit increase), 120 min OGTT (1.22, 1.08–1.38 for a 10-unit increase), an OGTT glucose peak at or after 60 min (1.92, 1.31–2.82), the number of islet autoantibodies (1.59, 1.24–2.03 for each additional antibody), positivity of ZnT8A (1.56, 1.00–2.43) and TSpan7A (1.62, 1.10–2.40), and obesity (2.45, 1.37–4.40). Furthermore, within the IA-2A–positive individuals, positivity against the IA-2β PTP epitopes (HR 1.74, 95% CI 1.06–2.88, $P = 0.021$) and the IA-2 JM epitopes (HR 1.75, 95% CI 1.11–2.77, $P = 0.015$) were associated with an increased rate of progression to stage 3. Age, sex, first-degree relative status, positivity for IAA, GADA, as well as 0-min and 30-min OGTT glucose values were not associated with the rate of progression to stage 3 (Supplementary Fig. 3). Each of the significant variables were individually added to the PLS parameters in the Cox proportional hazards model to determine whether they could improve the existing model. Only the addition of obesity improved the model ($P = 0.011$). Improvement was observed for those in the high and intermediate PLS categories (Supplementary Fig. 4).

Stratification of Progression Rates in Stage 1 Type 1 Diabetes Without an OGTT

OGTT values are not always available or can be impractical for study participants. It would, therefore, be helpful if stratification of risk within stage 1 type 1 diabetes could be performed without OGTT values. The factors that were significantly associated with progression to stage 3 type 1 diabetes in the univariate analysis were included in a stepwise Cox proportional hazards model without those derived from the OGTT. This yielded a multiple variable model that included the IA-2A categories (HR 1.52, 95% CI 1.25–1.85, $P < 0.0001$), HbA_{1c} (HR 2.09, 95% CI 1.04–4.20, $P = 0.040$), obesity (HR 2.18, 95% CI 1.20–3.96, $P = 0.010$), and positivity against JM epitopes (HR 1.57, 95% CI 1.01–2.45, $P = 0.046$) (Fig. 2*A*). The non–OGTT-based progression score developed from this model has an AUC of 0.798 in a ROC curve to identify those who progressed within 2 years (Supplementary Fig. 5). Thresholds of 1.25 and 3.0 stratified progression rates with 2-year risks of 1.7% (95% CI 0.0–3.7) for those with scores <1.25, 7.8% (2.1–13.3) with scores between 1.25 and 3.0, and 24.6% (12.0–35.4) for those with scores >3.0 ($P < 0.0001$) (Table 2 and Fig. 2*B*). In a sensitivity analysis, the non–OGTT-based progression score was applied to children who were classified as stage 1 based solely on a normal HbA_{1c} value, ignoring potentially elevated OGTT measurements. This yielded the following 2-year risks for progression to stage 3 type 1 diabetes: 3.3% (95% CI 0.7–5.8) for children with scores <1.25, 13.6% (6.7–19.9) for those with scores between 1.25 and 3.0, and 23.4% (11.8–33.4) for those with scores >3.0 ($P < 0.0001$) (Supplementary Fig. 6). Removal of the IA-2 JM epitope category from the model led to a slight loss in the model performance (AUC ROC curve, 0.752).

Stratification of Progression Rates by Original PLS in Stage 2 Type 1 Diabetes

Of the 85 Fr1da children with stage 2 type 1 diabetes at staging, 58 had a single dysglycemic abnormality (defined as impaired fasting glucose, impaired 2-h glucose after OGTT, impaired 30-min, 60-min, 90-min glucose after OGTT, or impaired HbA_{1c}), and 27 had two or more dysglycemic abnormalities. The 2-year risk for stage 3 type 1 diabetes was 30.2% (95% CI 17.9–42.5) and 68.0% (49.2–86.8), respectively ($P = 0.008$), over a median follow-up of 1.6 years (IQR 0.9–3.6) (Table 2). We, therefore, examined whether the PLS originally developed for stage 1 type 1 diabetes could stratify the 2-year risk in the 58 children with one abnormality stage 2 type 1 diabetes. A ROC curve analysis yielded an AUC of 0.680. A PLS threshold of 1.6 stratified the progression with 2-

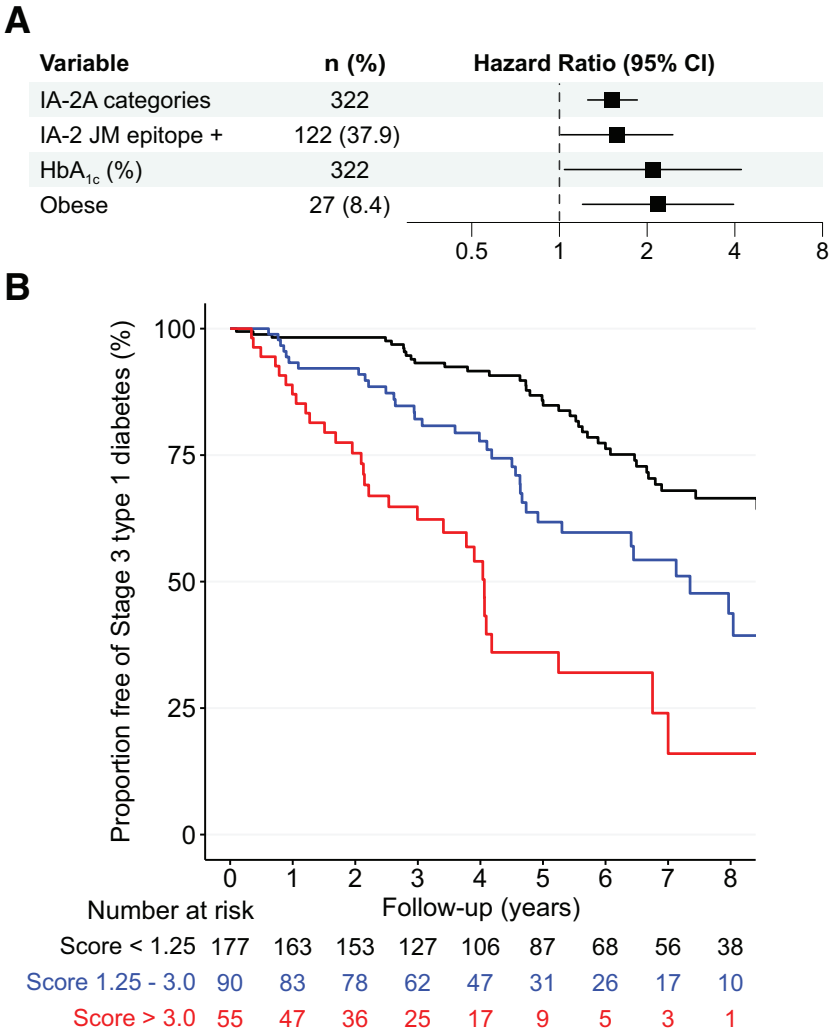

Figure 2—Development and performance of a non–OGTT-based progression score for stratification of progression from stage 1 to stage 3 type 1 diabetes. Variables significantly associated with the rate of progression to stage 3 in the univariable analysis were included in a stepwise multivariable Cox proportional hazards model analysis. *A*: The model selected four variables. The HRs (black squares) and the 95% CIs (lines) from the multivariable Cox proportional hazards model on 322 children with complete data are shown for each of the four variables. A score from the HRs was calculated for the 322 children. *B*: Kaplan-Meier survival curves for progression to stage 3 type 1 diabetes are shown for children with scores <1.25, 1.25–3.0, and >3.0. Progression differed significantly among categories ($P < 0.0001$). The numbers underneath the *x*-axis indicate the number remaining at each year of follow-up.

year risks of 42.4% (95% CI 22.8–57.0) in 35 children with values >1.6 and 5.6% (95% CI 0.0–15.6; $P = 0.002$) in 20 with values <1.6 (Table 2 and Fig. 3). Another 152 developed stage 2 type 1 diabetes with a single dysglycemic abnormality in follow-up. The PLS was also able to stratify risk of progression to stage 3 type 1 diabetes in these children with 2-year risks of 34.7% (95% CI 21.4–45.7) in the 72 with a PLS >1.6 and 5.1% (0.0–10.7) in the 61 with a PLS <1.6 ($P < 0.0001$) (Supplementary Fig. 7).

CONCLUSIONS

Assessment and stratification of the short- to moderate-term risk to develop clinical diabetes in individuals with early-stage type 1 diabetes is important for establishing monitoring schedules and for defining clinical trial or treatment eligibility criteria. Here, the previously developed PLS was shown to stratify risk in both current stage 1 and stage 2 type 1 diabetes as defined by ADA and consensus guideline (4,5) criteria. We further show in an exploratory proof-of-concept analysis that a score without the OGTT, but containing other parameters, is also able to stratify risk in children with stage 1 type 1 diabetes.

The PLS was developed for stratification within stage 1 type 1 diabetes (6). It was developed prior to the addition of elevated HbA_{1c} and 10% HbA_{1c} increase to the definition of stage 2 as well as a lowering of the FPG criteria. Therefore, a number of those previously identified as stage 1 are now classified as stage 2 type 1 diabetes. It was, therefore, important to determine whether the PLS and the previously defined PLS thresholds are still useful risk stratifiers. We used the Fr1da study cohort, which was extended in number and follow-up as well as a smaller validation cohort. As previously shown, a threshold of 0.5, corresponding to almost one-third of those with stage 1, was associated with no progression to stage 3 for at least 2 years. This is of value since these individuals require little monitoring over this period. Also of value, the previously defined threshold of 4.0, corresponding to the upper 12% of stage 1,

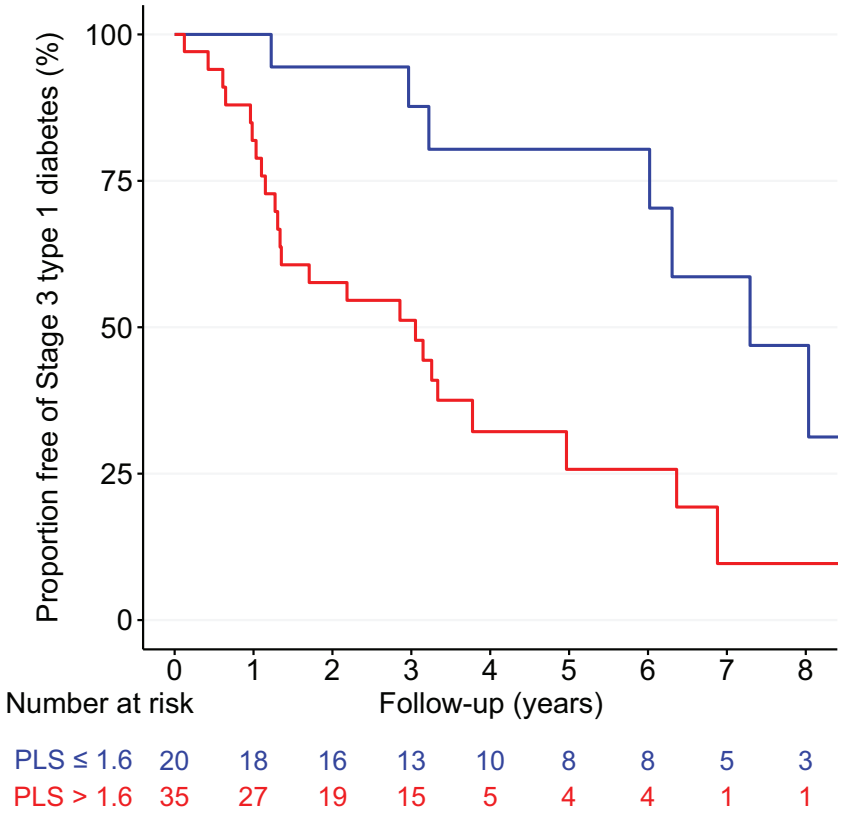

Figure 3—Stratification of progression from stage 2 to stage 3 type 1 diabetes by the PLS. Kaplan-Meier survival curves for progression to stage 3 type 1 diabetes in 55 children initially diagnosed with stage 2 type 1 diabetes in the Fr1da cohort, but having only one dysglycemic value. Children were categorized as those with a PLS ≤1.6 (n = 20) and those with a PLS >1.6 (n = 35). Progression differed significantly among categories ($P < 0.0001$). The numbers underneath the x-axis indicate the number remaining at each year of follow-up.

was associated with a >40% 2-year risk to develop stage 3 and identified most of those who progressed within 2 years. The risk in these children was not different from those who had stage 2 type 1 diabetes. We propose, therefore, that individuals with a high PLS should be monitored in a similar manner to those with stage 2 type 1 diabetes and should be considered for trials with intervention in stage 2.

Stage 2 type 1 diabetes is also heterogeneous (8). In particular, the risk of progression to stage 3 in those who have a single dysglycemic abnormality (such as one glucose elevation during OGTT or only an HbA_{1c} elevation) is substantially lower than in those with multiple dysglycemic abnormalities. Most (68%) of those with stage 2 had a single dysglycemic abnormality in our cohort. The PLS very effectively stratified risk in these individuals. In particular, a threshold of 1.6 identified one-third who had an associated 2-year risk for stage 3 type 1 diabetes of only 5%, while the remaining two-thirds had a risk that was >40%. The same threshold was able to stratify risk in stage 2 among the children and adolescents who developed their dysglycemia during follow-up, thereby validating the value of the PLS also in stage 2. Again, we suggest that monitoring and eligibility for clinical trials should consider the PLS of those with stage 2 type 1 diabetes.

The PLS is based on parameters usually included in recommended staging, such as OGTT, HbA_{1c}, and islet autoantibody level. This has the advantage that no additional measurements are required. The PLS was also effective in discriminating progression rates using IA-2A measured in two different assays. However, the PLS includes one parameter from the OGTT, a test that is not always performed or which can be difficult to execute, especially in young children. We, therefore, explored whether a score could be developed from non-OGTT parameters for stratification within stage 1. The model selected IA-2A titer categories and HbA_{1c}, both of which are in the PLS, and further selected obesity and autoantibody positivity for epitopes within the JM region of IA-2. In this proof-of-concept approach, the score could significantly stratify risk and, like the PLS, could identify those with low risk (<5%) within 2 years and moderate risk (>20%) within 2 years. A limitation of this analysis is that there was no validation cohort for this score. It nevertheless suggests that useful risk stratification within stage 1 type 1 diabetes can be performed with multiple parameters without OGTT. The two parameters that replaced the 90-min OGTT in this model were categorical and only indirectly related to glycemia. Obesity was infrequent in our cohort and was not associated with the 90-min OGTT value (data not shown). However, it was associated with a substantial increased risk for stage 3 type 1 diabetes in the few obese participants and, if validated, is a treatable condition. The IA-2A JM epitope reactivity is potentially interesting. Most of the epitopes in this region are within a short region spanning residues 610–631 (26), which forms the residual plasma membrane inserted portion that remains after cleavage at position 448 (extracellular domain) and 659 (intracellular PTP-like domain) (26). Although it is intracellular, it is likely to be a relatively unstructured region and remain within the plasma membrane longer than other IA-2 epitope regions. It may, therefore, be exposed when β-cells are destroyed, potentially explaining its association with a faster progression to stage 3. Assays that measure antibodies to the IA-2 JM epitopes are currently limited to an in-house RBA (22), but it is likely that assays, such as a Bridge-ELISA, can be developed.

The study has a number of limitations. An important limitation is that the Fr1da cohort and the validation cohort were both from Germany. It has, therefore, not been shown that the PLS has a similar performance in children and adolescents with stage 1 or stage 2 type 1 diabetes from other regions. The study did not include genetic markers or genetic scores associated with type 1 diabetes or other parameters such as proinsulin–to–C-peptide ratios (27–29), and it is possible that these could be valuable in risk models. Furthermore, several other parameters, such as

proteomic and transcriptomic markers (30–32), have the potential to enhance the ability to predict progression to stage 3 and, once standardized, may have additional value in a PLS. We have not examined whether simpler decision tree–based models and with categorical values for HbA_{1c} or OGTT parameters may be as effective as the PLS in stratifying early progression rates. The Fr1da cohort includes mainly children with European ancestry. It is, therefore, unknown whether the PLS stratifies progression rates in adults with early-stage type 1 diabetes or whether the PLS threshold applies to other ancestries. We have not assessed changes in the PLS over time and do not know whether changes in the PLS score are associated with variation in the progression rate to stage 3 type 1 diabetes. Finally, we have not compared the PLS with other models, including dynamic models or those based on machine-learning methods.

In conclusion, the PLS represents a relatively simple stratifier of short- to moderate-term risk of progression to stage 3 type 1 diabetes in children with early-stage disease. This or similar methods to stratify risk should be considered for guiding monitoring practices, counseling, and eligibility into clinical trials.

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