Supplementary Material

Islet Autoantibody Levels Differentiate Progression Trajectories in Individuals with Presymptomatic Type 1 Diabetes

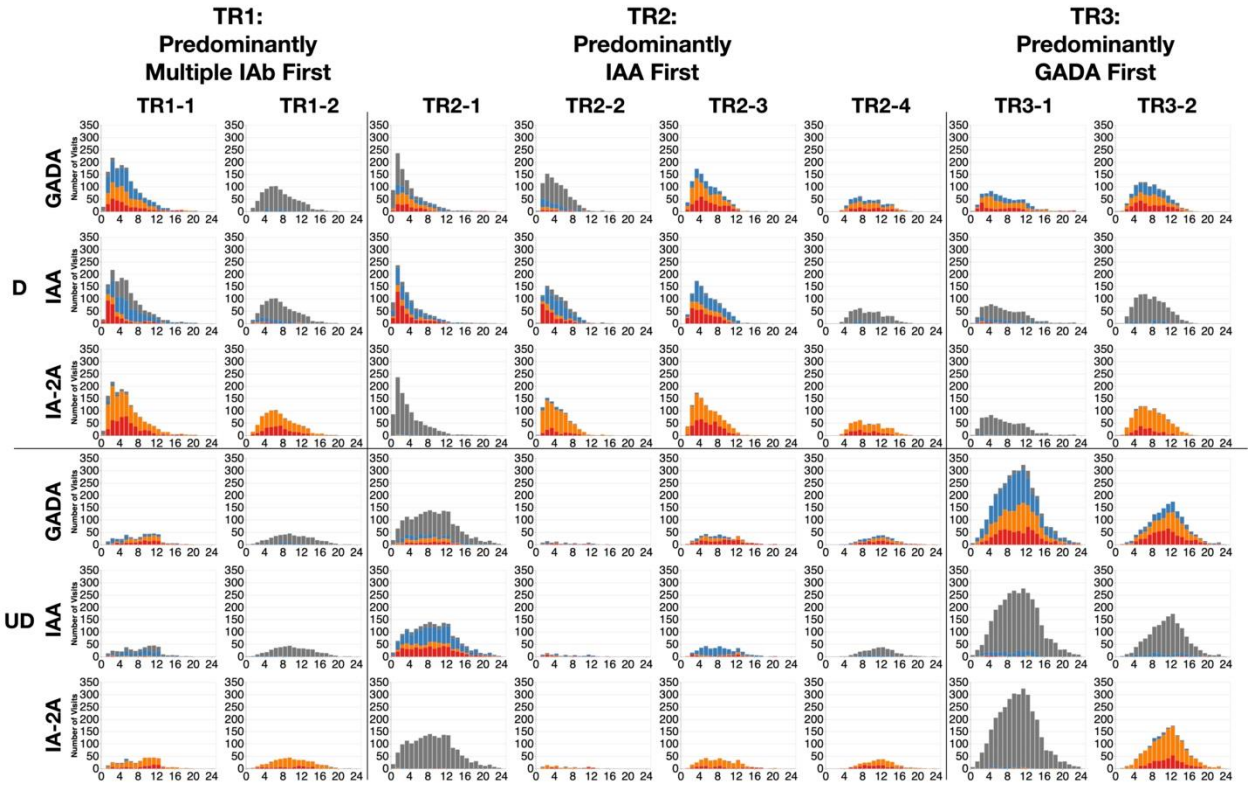
Bum Chul Kwon[1], Ph.D., Peter Achenbach[2], M.D., Vibha Anand[1], Ph.D., Brigitte I. Frohnert[3], M.D., Ph.D., William Hagopian[4], M.D., Ph.D., Jianying Hu[5], Ph.D., Eileen Koski[5], M.Phil., Åke Lernmark[6], Ph.D., Olivia Lou[7], Ph.D., Frank Martin[7], Ph.D., Kenney Ng[1], Ph.D., Jorma Toppari[8], M.D., Ph.D., Riitta Veijola[9], M.D., Ph.D., the T1DI Study Group.

[1]Center for Computational Health, IBM Research, Cambridge, MA, USA
[2]Institute of Diabetes Research, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich-Neuherberg, Germany
[3]University of Colorado, Denver, Colorado, USA
[4]Pacific Northwest Research Institute, Seattle, Washington
[5]Center for Computational Health, IBM Research, Yorktown Heights, NY, USA
[6]Department of Clinical Sciences Malmö, Lund University CRC, Skåne University Hospital, Malmö, Sweden
[7]JDRF International, New York, New York, USA
[8]Institute of Biomedicine and Centre for Population Health Research, University of Turku, and Department of Pediatrics, Turku University Hospital, Turku, Finland
[9]University of Oulu and Oulu University Hospital, Department of Pediatrics, PEDEGO Research Unit, Medical Research Center, Oulu, Finland

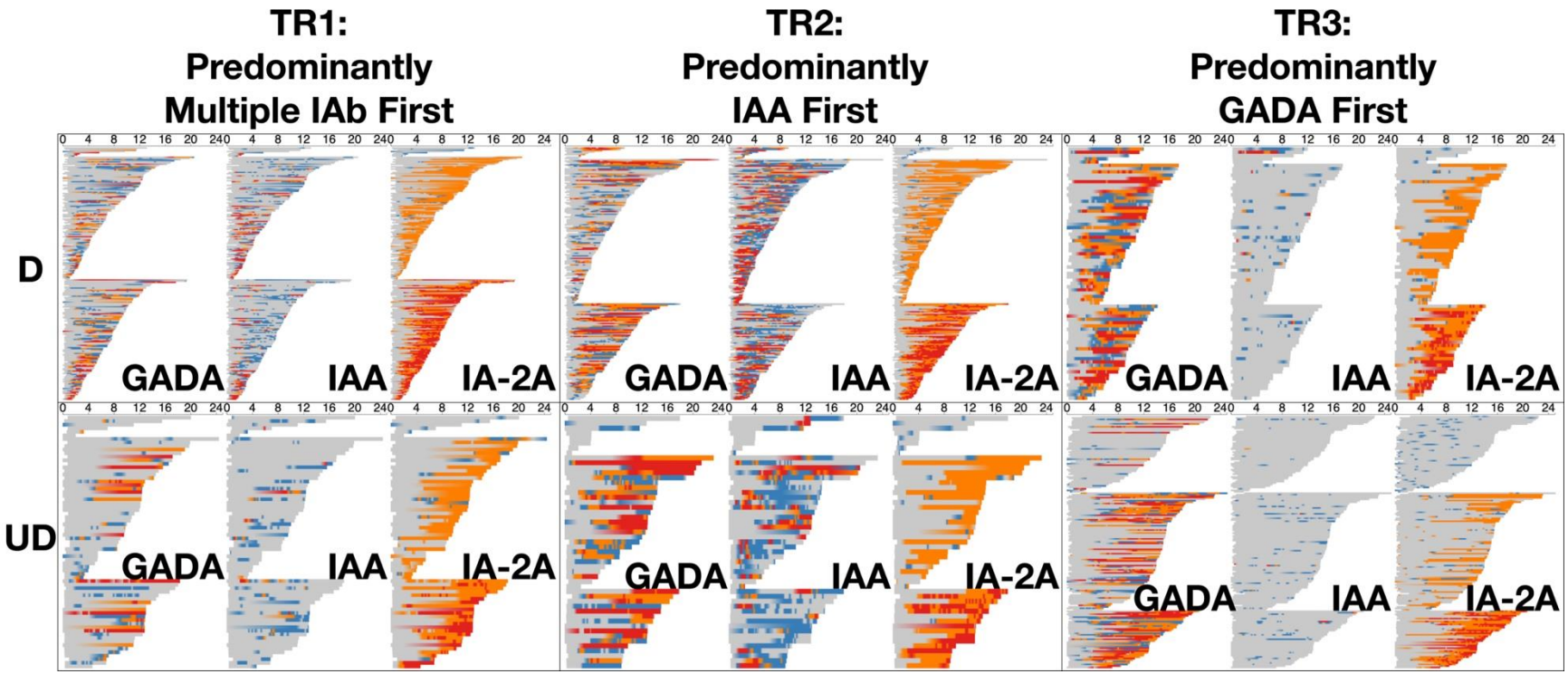
Corresponding Author:

Bum Chul Kwon, Ph.D.
Research Staff Member
IBM Research
314 Main Street, Cambridge, MA, 02142
Tel: 1-617-492-9300
Email: bumchul.kwon@us.ibm.com

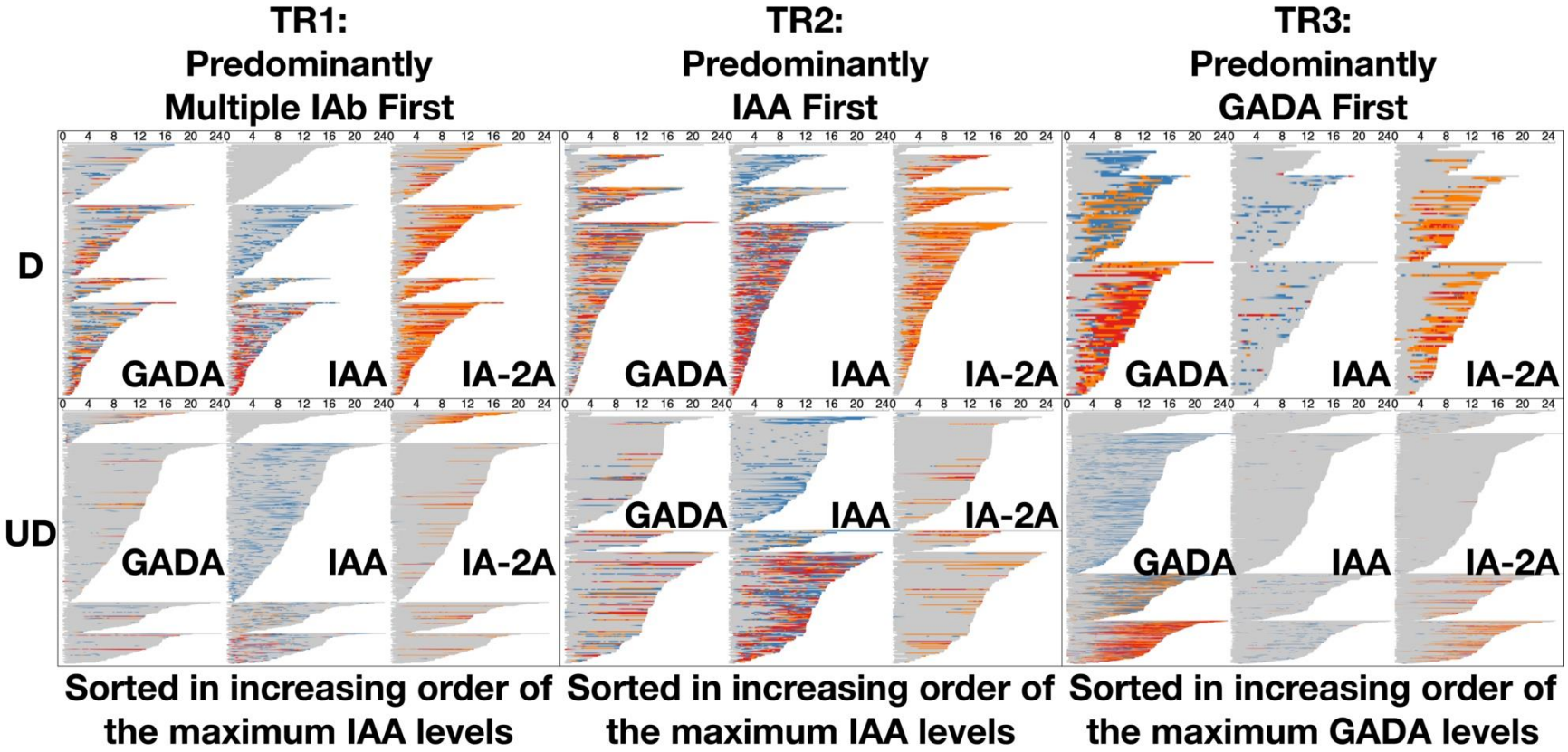
Supplementary material includes:
Supplementary Figures 1-6
Supplementary Tables 1-2



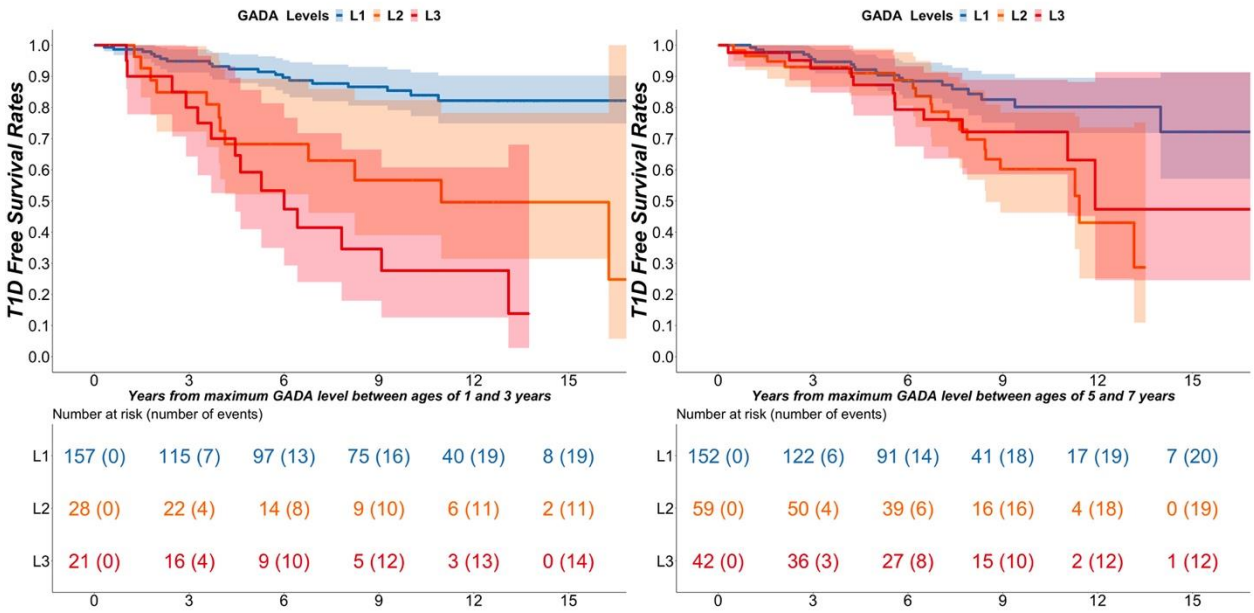
Supplementary Figure 1. 1. Proportions of autoantibody levels at each visit by age comparing diagnosed and undiagnosed individuals. The diagram shows 48 panels (6 rows, 8 columns) summarizing the proportion of autoantibody levels over participants' age per 8 IAb positive states (TR1-1, TR1-2, TR2-1, TR2-2, TR2-3, TR2-4, TR3-1, TR3-2) and the IAb type (GADA, IAA, IA-2A). For example, TR1-1 indicates the first positive component state of trajectory TR1, predominantly multiple islet autoantibodies first. Each panel includes a stacked bar chart that shows the total number of visits (y-axis), which are broken down into stacks of four autoantibody levels and missing data IAb levels (L0: Gray, L1: Blue, L2: Orange, L3: Red), over ages of participants (x-axis).



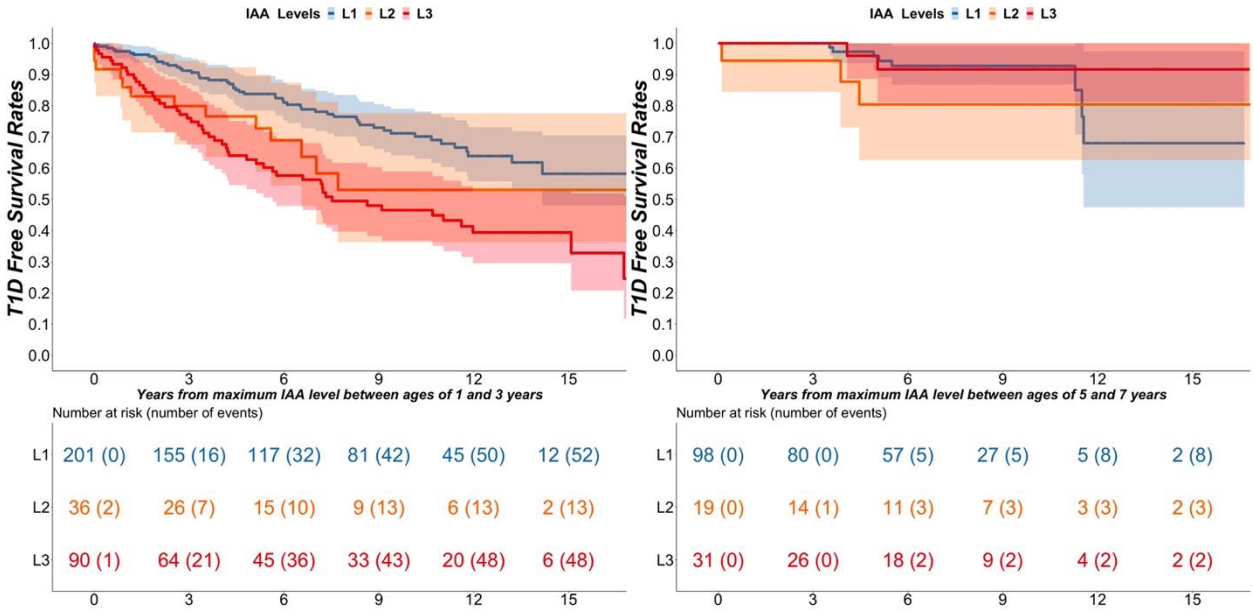
Supplementary Figure 2. 2. Development of islet autoantibody levels for individual sorted by maximum IA-2A level. The diagram includes six panels (2 rows and 3 columns) summarizing the dwell time of individual participants at each autoantibody level (L0: Gray, L1: Blue, L2: Orange, L3: Red) for three islet autoantibodies (GADA, IAA, IA-2A) over their ages (x-axis) per trajectory (column) and per diagnosis (row). In each panel, we sorted participants (bars) by the maximum level of IA-2A with increasing level from top to bottom. We excluded those who only reached L0 of IA-2A from this figure.



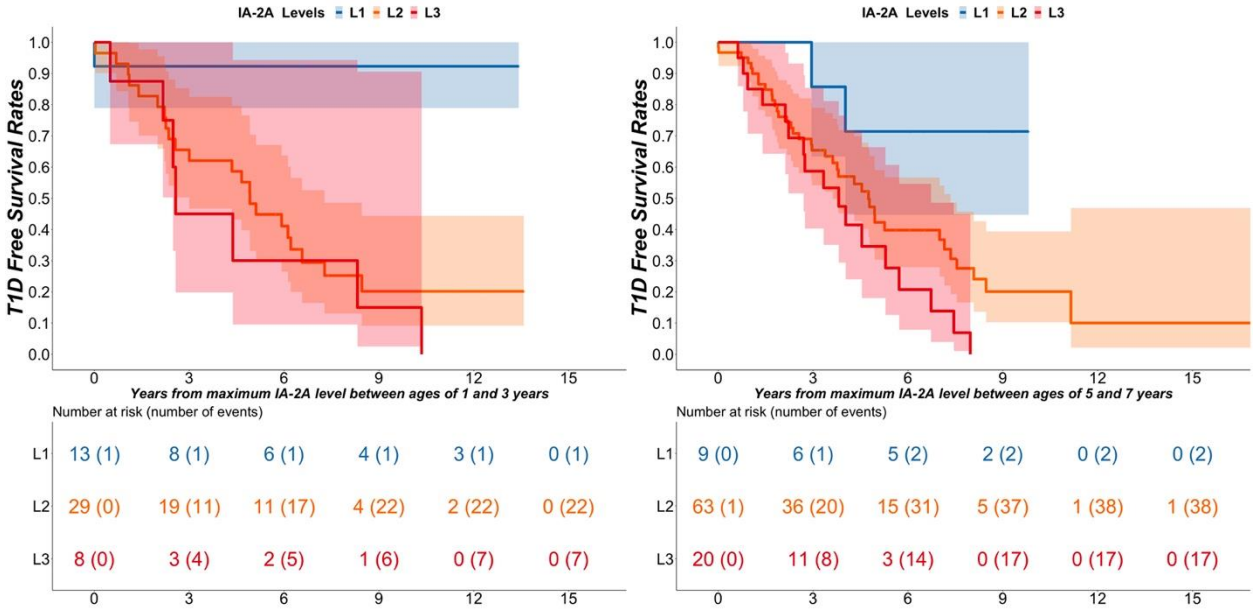
Supplementary Figure 3. 3 Development of islet autoantibody levels for individual participants sorted by maximum IAA or GADA level. The diagram includes six panels (2 rows and 3 columns) summarizing the dwell time of individual participants at each autoantibody level (L0: Gray, L1: Blue, L2: Orange, L3: Red) for three islet autoantibodies (GADA, IAA, IA-2A) over their ages (x-axis) per trajectory (column) and per diagnosis (row). Participants in each trajectory (column) are sorted by the maximum level of IAA for TR1 and TR2, and of GADA for TR3 with increasing level from top to bottom.



Supplementary Figure 4. Diabetes-free survival curves (mean and 95% confidence intervals) of the participants who had GADA only positivity at the age of 2 years (Left) and 6 years (Right), stratified by GADA positivity levels (L1, L2, L3). Participants with GADA L2 and L3 at age 2 years progressed faster to diabetes than those with GADA L1 ($p < .001$). At age 6 years, participants with GADA L2 progressed faster to diabetes than those with GADA L1 ($p = .012$).



Supplementary Figure 5. Diabetes-free survival curves (mean and 95% confidence intervals) of the participants who had IAA only positivity at the age of 2 years (Left) and 6 years (Right), stratified by IAA positivity levels (L1, L2, L3). Participants with IAA L3 at age 2 years progressed faster to diabetes than those with IAA L1 ($p < .001$). Participants with IAA L2 at age 2 progressed marginally faster to diabetes than those with IAA L1 ($p = .056$). No differences were observed in the progression rates between participants with IAA L1, L2, or L3 at age 6 years.



Supplementary Figure 6. Diabetes-free survival curves (mean and 95% confidence intervals) of the participants who had IA-2A only positivity at the age of 2 years (Left) and 6 years (Right), stratified by IA-2A positivity levels (L1, L2, L3). Participants with IA-2A L2 and L3 at age 2 years progressed faster to diabetes than those with IA-2A L1 ($p < .01$). Participants with IA-2A L3 at age 6 years progressed faster to diabetes than those with IA-2A L1 ($p = .014$).

Supplementary Table 1. The number of samples analyzed for islet autoantibodies at various ages of the 2,145 autoantibody positive participants.

Age	All	Diagnosed	Undiagnosed
0 - 1	4126	1381	2745
1 - 2	4180	1397	2783
2 - 3	3667	1280	2387
3 - 4	3361	1170	2191
4 - 5	3182	1089	2093
5 - 6	3043	1011	2032
6 - 7	2717	836	1881
7 - 8	2523	690	1833
8 - 9	2436	590	1846
9 - 10	2256	494	1762
10 - 11	2084	415	1669
11 - 12	1985	341	1644
12 - 13	1739	237	1502
13 - 14	1283	162	1121
14 - 15	1041	102	939
15 - 16	695	57	638
16 - 17	370	50	320
17 - 18	268	26	242
18 - 19	212	18	194
19 - 20	132	13	119
20 - 21	110	7	103
21 - 22	69	5	64
22 - 23	49	5	44
23 - 24	23	0	23
24 - 25	13	1	12
25 - 26	2	0	2
26 - 27	4	0	4

Supplementary Table 2. Demographic data and sampling intervals of the 2,145 autoantibody positive participants in the five study sites.

Study Sites	Number of Female Participants	Number of Male Participants	Sampling Intervals in Years Median (IQR)	Number of Participants in TR1	Number of Participants in TR2	Number of Participants in TR3
BABYDIAB	123	124	0.57 (0.22 to 1.10)	70 (28.3%)	91 (36.8%)	86 (34.8%)
DAISY	127	153	0.55 (0.31 to 1.00)	105 (37.5%)	52 (18.6%)	123 (43.9%)
DEW-IT	25	37	0.50 (0.30 to 1.17)	35 (56.5%)	15 (24.2%)	12 (19.4%)
DIPIS	196	183	0.86 (0.23 to 1.06)	127 (33.5%)	57 (15.0%)	195 (51.5%)
DIPP	484	693	0.31 (0.25 to 0.51)	402 (34.2%)	315 (26.8%)	460 (39.1%)