

1 **Islet Autoantibody Screening in Adolescents at Risk to Predict Type 1 Diabetes Until**
2 **Young Adulthood: a prospective cohort study**

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36 **Main text 2848 words, Summary 319 words, Display items 5 (one table and four figures),**

37 **References 32.**

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39 **Summary**

40 **Background** Screening for islet autoantibodies identifies individuals who will later develop type
41 1 diabetes, allowing patient and family education to prevent diabetic ketoacidosis at onset and to
42 enable consideration of prevention therapies. There is lack of knowledge about effective islet
43 autoantibody screening for diabetes risk among adolescents.

44 **Methods** Data were harmonized from prospective studies from Finland (DIPP), Germany
45 (BABYDIAB), and the USA (DAISY and DEW-IT) comprising a total of 20,303 children with
46 increased type 1 diabetes risk. Children under age 10 who were lost to follow-up or diagnosed
47 with type 1 diabetes were excluded. Inverse probability censoring weighting was used to include
48 data from all 8,682 remaining participants. Autoantibodies to insulin, glutamic acid
49 decarboxylase, and insulinoma antigen-2 were measured at each follow-up visit. Sensitivity and
50 positive predictive value (PPV) of these autoantibodies, tested at one or two ages, to predict type
51 1 diabetes by age 18 were the primary outcomes.

52 **Findings** Of 8682 adolescents studied, 1890 were followed to age 18 years or developed
53 diabetes between ages 10 and 18. Their median follow-up was 18.3 years [IQR 14.5-20.3]. A
54 total of 442/1890 were positive for ≥ 1 islet autoantibody and 262/1890 developed diabetes. Time
55 from seroconversion to diabetes increased by 0.64 years (95% CI 0.34-0.95) for one year
56 increment of diagnosis age. Of diabetes cases, 227 were autoantibody positive and 35 had no
57 detected autoantibodies within median time of 0.3 and 6.8 years from last pre-diagnostic sample,
58 respectively. Single screening at age 10 was 90% sensitive (95% CI 86-95) with PPV of 66%
59 (95% CI 60-72) for clinical diabetes. Screening at two ages (10 and 14 years) increased
60 sensitivity to 93% (95% CI 89-97) but lowered PPV to 55% (95% CI 49-60).

61 **Interpretation** Screening of adolescents at risk for type 1 diabetes only once at age 10 for islet
62 autoantibodies was highly effective to detect diabetes by age 18, to prevent ketoacidosis and
63 enable prevention therapies.

64 **Funding** JDRF International

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66 **Research in context**

67 **Evidence before this study**

68 We searched PubMed with search terms “screening”, “autoantibod*”, “prediction”, “type 1
69 diabetes”, and “child*” for articles published until July 5, 2022. Several prospective studies have
70 followed young, genetically susceptible children from birth or young individuals with a family
71 member having type 1 diabetes for the development of islet autoantibodies. Confirmed positivity
72 for multiple islet autoantibodies predicts almost inevitable progression to clinical diabetes within
73 15 years from seroconversion although the lag time from islet autoimmunity to diabetes is highly
74 variable. Young age at seroconversion is associated with faster progression rate compared to
75 older age. Furthermore, the annual incidence of islet autoantibodies declines as the child gets
76 older, at least in individuals with high HLA-conferred susceptibility for type 1 diabetes. Recent
77 analyses from prospective follow-up studies of children at increased genetic risk for type 1
78 diabetes indicate that two-age screening, at 2 years and 5-7 years, effectively identifies
79 individuals developing childhood type 1 diabetes. However, no published data exist about
80 optimal screening strategy for islet autoimmunity in adolescents aged between 10 and 18 years.

81 **Added value of this study**

82 We observed that double screening at age 10 years and 14 years, or even single screening at age
83 10 years, was highly sensitive to detect adolescents who will develop type 1 diabetes. On the
84 other hand, almost no one who remained islet autoantibody negative at these screening ages
85 developed diabetes.

86 **Implications of all the available evidence**

87 Islet autoantibody screening in adolescents effectively identifies individuals at increased risk to
88 develop type 1 diabetes and therefore, may allow prevention of diabetic ketoacidosis. These

89 young people may also have possibility to take part in secondary prevention trials. Furthermore,
90 these data will be important for the on-going islet autoantibody screening programmes in the
91 general population. Future research should validate these optimal screening age(s) in other
92 unselected adolescent populations and potentially also adult populations.

93

94 **Introduction**

95 Type 1 diabetes is preceded by the appearance of islet autoantibodies that have been used
96 successfully as biomarkers of disease risk¹. Screening for islet autoimmunity in the general
97 population or in genetically susceptible subpopulations has allowed identification of subjects for
98 type 1 diabetes prevention trials, e.g., in TrialNet, GPPAD, and INNODIA. Follow-up of
99 individuals who have tested positive for one or multiple islet autoantibodies has also helped to
100 prevent occurrence of diabetic ketoacidosis at the time of diabetes diagnosis²⁻⁶. We have
101 previously analysed optimal screening strategy in young children in the Type 1 Diabetes
102 Intelligence (T1DI) Consortium that combined data from multiple birth cohort studies which
103 followed children through adolescence with regular islet autoantibody measurements to identify
104 individuals with a high risk to develop the disease⁷. However, the appearance of autoantibodies
105 and the time from that to clinical type 1 diabetes is age-dependent⁷⁻¹⁰. The youngest children tend
106 to first develop autoantibodies against insulin (IAA) and progress more quickly to clinical
107 diabetes than older children with IAA as the first appearing autoantibody. Additionally, older
108 children more often develop glutamic acid decarboxylase antibodies (GADA) as the first
109 autoantibody and their progression to diabetes is less dependent on initial seroconversion age⁸.
110 Therefore, we hypothesised that optimal screening strategy for older children may differ from
111 that for younger children. We present here an analysis focused on adolescents, to find out
112 optimal islet autoantibody screening strategy for effective identification of subjects at risk of
113 type 1 diabetes between 10 and 18 years of age.

114

115 **Methods**

116 **Study Design and Cohort**

117 The T1DI cohort includes a total of 24,662 participants from five prospective studies: the Finnish
118 Type 1 Diabetes Prediction and Prevention (DIPP) study¹¹, the Swedish Diabetes Prediction in
119 Skåne Study (DiPiS)¹², the Diabetes Autoimmunity Study in the Young (DAISY)¹³ from
120 Colorado, USA, the Diabetes Evaluation in Washington (DEW-IT)¹⁴ from Washington State,
121 USA and BABYDIAB¹⁵ from Germany. Approvals from the local ethics committees were
122 obtained, and informed consents for all participants were received from the parents and/or
123 adolescents, as well as adolescent assents when relevant. DiPiS subjects (n=4359) were not
124 included in the current analysis because little follow-up data on them was available for the age
125 range considered in the present study. All subjects from the BABYDIAB, DAISY, DEW-IT and
126 DIPP studies, who were followed up to age 18 years or beyond, were included, and all their visits
127 from the start of follow-up were considered. For these individuals, only information of visit(s)
128 that occurred after age 10 was used when estimating screening performance. In other words, we
129 wanted to simulate a screening situation that is focused on individuals aged 10-18 years and who
130 have no prior information on islet autoimmunity. Thus, we excluded individuals who were
131 diagnosed with type 1 diabetes or lost to follow-up before age 10 because there was no
132 information from them between ages 10 and 18. Data of subjects who were lost to follow-up
133 between age 10 and 18 years were utilized in data analysis using inverse probability censoring
134 weighting (IPCW) method as detailed in the Statistical Analyses section. Thus, data from a total
135 of 8682 subjects were included. Of the total T1DI cohort, 1890 participants were followed
136 through age 18 or diagnosed between ages 10 and 18 (figure S1). Their median follow-up time
137 from age 10 until the end of follow-up or diagnosis of diabetes was 9.9 years (IQR 8.1-11.4).

138 HLA groups A, B, C, and D were defined as previously reported^{1,7}. Based on Type 1 Diabetes
139 Genetics Consortium data, the approximate Odds Ratios for type 1 diabetes are >50 in group A,
140 11-32 in Group B, 4-10 in Group C and 0.1-3.0 in group D¹⁶. Seroconversion was defined as
141 detection of the same islet autoantibody in two consecutive visits of which the first one
142 designated as the time of seroconversion.

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144

145 **Analyses of islet autoantibodies**

146 Autoantibodies against insulin, glutamic acid decarboxylase and insulinoma antigen 2 (IA-2A)
147 were measured by radiobinding assays validated in international workshops and described earlier
148 in detail by the T1DI Study Group¹.

149 **Outcomes**

150 The main outcomes were sensitivity and positive predictive value (PPV) of the presence of any
151 islet autoantibody at a given age or at two ages for type 1 diabetes prediction by age 18.
152 Specificity and negative predictive values were also calculated.

153 **Statistical Analyses**

154 We used islet autoantibody test results of samples measured within a window of six months
155 before and after the indicated subject age. If several samples were analysed within the time
156 window of 12 months, the result closest to the indicated age was considered. The subjects were
157 then designated as positive for at least one islet autoantibody (IAA, GADA or IA-2A), negative
158 for all three autoantibodies, or without a test result if no measurement was available within the
159 target window. We considered screening at a single or two ages from 10 to 18 years, and each
160 screening test was evaluated using time dependent metrics for sensitivity and positive predictive

161 value (PPV)¹⁷. We calculated cumulative sensitivity¹⁷ where diagnosed subjects with missing
162 tests were included in the denominator when calculating sensitivity to allow comparison of all
163 age pairs, referred herein as comparative sensitivity. The optimum screening ages from the
164 comparative sensitivity were then evaluated among children completing testing and observation
165 and is referred herein as observed sensitivity. To account for right censored subjects who were
166 lost from follow up before age 18, we used inverse probability censoring weighting, IPCW¹⁸.
167 The 95% confidence intervals for sensitivities and positive predictive values at various screening
168 ages were computed as $\text{mean} \pm 1.96 * \text{SD}$ from 10,000 bootstrap samples with replacement.
169 Pearson's correlation was used to calculate the possible correlation between time from
170 seroconversion to diagnosis of type 1 diabetes and age at diabetes diagnosis.

171

172 **Role of the funding source:** JDRF International, the non-profit funder of the study, supported
173 the creation of the harmonised T1DI dataset and the data analyses. Two JDRF employees
174 worked in the team that analysed and interpreted the data and developed the report.

175

176 **Results**

177 In the cohort of 1890 participants, a median of 16 samples [interquartile range IQR 10-21] per
178 participant were analysed for islet autoantibodies. The median duration of prospective follow-up
179 was 18.3 years [IQR 14.5-20.3] and the median age of diabetes diagnosis was 12.6 years [IQR
180 11.2-15.0]. Family history of type 1 diabetes (positive or negative) was reported in 59.2%
181 (n=1119) of the subjects. The proportion of subjects with high-risk HLA (group A and B) was
182 54.1% (n=1023). The remaining subjects carried lower HLA risk (group C and D). The majority
183 of subjects were followed from young ages to age 18 and those who seroconverted did so at a
184 median age of 7.1 years [IQR 4.0-10.5] (table). Most of the 1890 subjects did not seroconvert
185 and did not develop type 1 diabetes (light blue group in figure 1). There were 215 subjects
186 (11.4%) who seroconverted but did not progress to diabetes within the follow-up period (dark
187 blue group in figure 1). A total of 227 subjects (12.0%) had a seroconversion at median age of
188 5.0 years and developed type 1 diabetes at median age of 12.7 years (red group in figure 1). A
189 small group of participants developed type 1 diabetes without identified seroconversion (orange
190 group in figure 1). Median interval between the last pre-diagnostic sample and the diagnosis was
191 0.3 years [IQR 0.1, 1.3] for autoantibody positive cases, whereas it was 6.8 years [IQR 1.6, 9.9]
192 for the 35 autoantibody negative ones.

193 The number of subjects from each source study is shown in figure 2A. The DEW-IT Study
194 recruited older children than the three other studies, whilst the number of children in the DIPP
195 Study declined towards the end of the observation period, because many children were diagnosed
196 before the age of 10 and the follow-up of autoantibody negative children ended at age 15. A vast
197 majority of those who seroconverted, did so before age 10 and in the DIPP study even before age
198 6 (figure 2B). The cumulative number of islet autoantibody positive children in the follow-up

199 increased steadily until 12 years of age, after which the number declined due to onset of diabetes
200 and the end of autoantibody screening at age 15 years in some cohorts (figure 2C). The number
201 of subjects with newly diagnosed type 1 diabetes was highest between the ages of 10 and 12
202 (figure 2D). The median time from seroconversion to diabetes increased by age at diagnosis,
203 although individual variation remained wide (figure 3). The median time between seroconversion
204 and diagnosis increased by 0.64 years (95% CI 0.34-0.95) for one year increase in diagnosis age
205 (Pearson correlation coefficient 0.88, 95% CI 0.50-0.97, $p=0.002$).

206 When screening at a single age was considered, screening at age 10 showed the highest
207 comparative sensitivity of 63% (95% CI 56-70) (figure 4A). The corresponding positive
208 predictive value was 39% (95% CI 32-46) (figure 4B). Specificity was 38% (95% CI 36-40)
209 (figure S2). When screening was performed twice, at ages 10 and 14, comparative sensitivity
210 improved to 72% (95% CI 65-78), but positive predictive value decreased to 29% (95% CI 24-
211 34). Specificity was 63% (95% CI 61-66). The negative predictive value was 99-100% for all
212 single age and pair-wise screening time points (figure S3). Figure 4 summarizes the sensitivities
213 and positive predictive values of islet autoantibody screening at all different single ages between
214 10 and 17 years and with different pair-wise combinations of two screening time points. Sex-
215 specific comparative sensitivities were relatively similar for the males and females, but the
216 positive predictive values were slightly higher for the males (figure S4).

217 When evaluating only children completing both testing and observation, the observed sensitivity
218 for screening at a single age of 10 years was very high at 90% (95% CI 86-95) with a PPV of
219 66% (95% CI 60-72). For screening at the two ages of 10 and 14 years, observed sensitivity
220 increased to 93% (95% CI 89-97), but the PPV decreased to 55% (95% CI 49-60).

221

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Discussion

223 To our knowledge, there are few published studies focusing on islet autoantibody screening in
224 adolescents¹⁹. The large multinational T1DI cohort made it possible to analyse different
225 screening strategies in a cohort where many subjects were followed through age 18. The present
226 analysis shows that single islet autoantibody screening at the age of 10 is an effective way to
227 identify adolescents at high risk to develop type 1 diabetes. Screening twice at ages 10 and 14
228 improves sensitivity only marginally. Given that the cost of two-age screening is twice that of a
229 single screening, we consider a single screening at age 10 a good choice. However, the
230 acceptability of islet autoantibody screening by the families, adolescents, and clinicians are also
231 important factors to consider when planning screening programmes for islet autoimmunity.
232 Single testing may be more economical and more acceptable but this needs to be evaluated in the
233 setting of each specific country. The cost of islet autoantibody screening might also be affected
234 by the possibility to integrate it with ongoing pediatric health surveillance programmes. Future
235 studies are needed to clarify these questions. Furthermore, combining genetic risk score
236 including non-HLA risk variants with islet autoantibody screening could be even more effective
237 way to identify most individuals who develop type 1 diabetes in the future²⁰.

238 When considering the entirety of childhood, initiation of islet autoimmunity peaks at an early age
239 of one to two years. Those with early seroconversion tend to develop diabetes faster than those
240 with later appearing autoimmunity^{21,22}. We previously showed that screening of children at two
241 and six years of age effectively identifies most who develop type 1 diabetes before 15 years of
242 age⁷. The present analysis provides a framework for screening of older children and adolescents
243 which is meaningful for several important reasons. First, establishing the safety of
244 immunotherapeutic drugs to prevent or delay clinical type 1 diabetes necessarily involves testing

245 in adults, then moving to adolescents, then to younger children, so identifying relevant cohorts of
246 adolescents is important for the middle stage of this process²³. It has been challenging to find
247 participants for such trials²⁴. Second, the American Academy of Pediatrics recommends
248 pediatric screening for hypercholesterolemia between the ages of 9 and 11, and this represents
249 one of the few childhood ages where a routine blood sample is likely to be collected²⁵. Third, it is
250 noteworthy that diabetic ketoacidosis at the time of diagnosis of type 1 diabetes occurs most
251 often in two risk age groups, toddlers and teenagers²⁶. Presence of a family member with type 1
252 diabetes is known to reduce the risk of diabetic ketoacidosis at diagnosis²⁷. Screening for islet
253 autoimmunity helps to direct education and glycemic monitoring to the group with the highest
254 risk to develop type 1 diabetes, which is highly likely to further reduce the incidence of
255 ketoacidosis^{4,5,28}.

256 To compare performance of various two-age screening pairs in a dataset with variable numbers
257 of subjects tested at each specified age, comparative sensitivities using the cumulative sensitivity
258 method¹⁷ were calculated by including also cases with missing tests in the denominator. This was
259 necessary to allow comparison of screening results from all age pairs (Figures 4 and S4).
260 However, it led to lower sensitivity estimates than the observed sensitivity which considered
261 only subjects actually tested at the specified ages. Therefore, once the optimum strategy was
262 identified by comparative method, the actual observed sensitivity was determined using subjects
263 tested at the optimum timepoint(s) and observed during the follow-up period. A limitation of this
264 approach might be that we cannot rule out some bias originating from the distribution of non-
265 tested cases within the cumulative sensitivity calculation, but this was the best available method
266 to compare age pairs and revealed high sensitivity and positive predictive value in direct
267 observation.

268 In the past it has been shown that learning about the child's increased genetic risk for type 1
269 diabetes induces only mild anxiety in most parents²⁹. A cohort study by Johnson et al. showed
270 that any islet autoantibody positivity in children increased parental anxiety but anxiety decreased
271 constantly during the 4-year follow-up³⁰. However, a significant proportion up to 43% of the
272 parents were still reporting high scores of anxiety after three years of follow-up³⁰. In another
273 study, other family life stressors were found to be more substantial than becoming aware of
274 autoantibody positivity³¹. It remains to be investigated whether awareness of autoantibody
275 positivity affects general well-being and development of adolescents themselves.

276 Strengths of the present analysis include a large dataset of adolescents from three different
277 countries and systematic screening for islet autoantibodies and follow-up of autoantibody
278 positive subjects through age 18. Data from all participants with any visit after age 10 were
279 utilized by applying the inverse probability censoring weighting, thereby reducing the potential
280 bias caused by non-random loss to follow-up. Our study subjects represent a wide variation of
281 class II HLA genotypes more broadly representative of the full spectrum of type 1 diabetes than
282 many similar studies¹. However, a limitation is that up to 59% of the participants were first
283 degree relatives of patients with type 1 diabetes. Therefore, these results should be replicated in
284 an unselected adolescent population because the best age for screening in the general population
285 could be different from what is shown in the population of the current study. The ultimate aim
286 should be to establish a global screening strategy for the risk of type 1 diabetes and include also
287 children and adolescents of non-European ancestries. Childhood T1D is most prevalent in
288 northern European populations. The current results can first be applied in these countries. On the
289 other hand, elsewhere the childhood populations are much larger and although T1D incidence is
290 low, screening for islet autoimmunity could save larger numbers of children from DKA. This

291 necessitates new studies in populations of non-European ancestries. Autoantibodies against zinc
292 transporter 8 were not included because they were not measured systematically in the original
293 cohorts, and future studies should include them, too. Another limitation is rather short follow-up
294 time beyond age 18 years, which was reflected by modest PPVs for the screening, particularly
295 when islet autoantibody screening of the older adolescents was considered. If the follow-up were
296 longer, the PPVs would certainly increase because of accumulating number of type 1 diabetes
297 diagnoses in adulthood, albeit slowly. The original studies focused on early ages because they
298 were performed in the framework of paediatric and adolescent medicine. Since the majority of
299 new cases with type 1 diabetes are actually diagnosed at adult age³² future research should
300 include extended follow-up after adolescent screening to include more complete outcome data.
301 However, for the time being the present report remains the best estimate for optimal screening of
302 islet autoantibodies in adolescents.

303 In conclusion, this study shows the importance of screening for islet autoantibodies at least once
304 at age 10 years to predict future type 1 diabetes. Since individuals with increased genetic or
305 familial risk are known to have higher future risk for type 1 diabetes, screening may be
306 particularly important in these groups also during adolescence. We believe these results provide
307 a pragmatic, highly efficient strategy for islet autoantibody screening that would facilitate
308 prevention of diabetic ketoacidosis and recruitment of young people into new prevention trials.
309 Future studies should identify the optimal screening strategy for the general adolescent
310 population.
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~~321~~**Contributors**

323 All authors contributed to the design of the study analysis. MG performed data analyses and takes

324 responsibility for the accuracy of the results. The PIs of the original studies (WH, MR, A-GZ, RV)

325 are responsible for verification of the underlying data. RV, JT, WH and MG wrote the manuscript.

326 All authors contributed to the discussion, editing, and review of the manuscript and approved the

327 final version.

~~328~~**Declaration of interests**

330 MG and VA are employees of IBM. FM and OL performed this work as employees of JDRF. All

331 other authors declare no competing interests.

~~332~~**Data sharing**

334 The data that support the findings of this study are available through the Type 1 Diabetes

335 Intelligence Consortium upon request to the corresponding author. The data are not publicly

336 available due to privacy regulations.

337

Acknowledgments

338 We thank the participating children and families, and the personnel of the study sites. This work

339 was supported by funding from JDRF (IBM: 1-RSC-2017-368-I-X, 1-IND-2019-717-I-X,

340 DAISY: 1-SRA-2019-722-I-X, 1-RSC-2017-517-I-X, 5-ECR-2017-388-A-N, DIPP: 1-RSC-

341 2018-555-I-X, 1-SRA-2019-721-I-X, and DEW-IT: 1-SRA-2019-719-I-X, 1-RSC-2017-516-I-

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432

	The entire cohort	Seroconversion and type 1 diabetes	No seroconversion but type 1 diabetes	Seroconversion but no type 1 diabetes	No seroconversion and no type 1 diabetes
Number of subjects, n (%)	1890	227 (12.0%)	35 (1.9%)	215 (11.4%)	1413 (74.8%)
Data Source					
DIPP	203 (10.7%)	116 (51.1%)	9 (25.7%)	45 (20.9%)	33 (2.3%)
DAISY	599 (31.7%)	46 (20.3%)	12 (34.3%)	50 (23.3%)	491 (34.7%)
DEWIT	304 (16.1%)	27 (11.9%)	8 (22.9%)	50 (23.3%)	219 (15.5%)
BABYDIAB	784 (41.5%)	38 (16.7%)	6 (17.1%)	70 (32.6%)	670 (47.4%)
Sex					
Female	918 (48.6%)	84 (37.0%)	13 (37.1%)	106 (49.3%)	715 (50.6%)
T1D Family History					
Yes	1119 (59.2%)	79 (34.8%)	16 (45.7%)	105 (48.8%)	919 (65%)
..No	568 (30.1%)	32 (14.1%)	10 (28.6%)	65 (30.2%)	461 (32.6%)
Unknown	203 (10.7%)	116 (51.1%)	9 (25.7%)	45 (20.9%)	33 (2.3%)
HLA Group*					
A	348 (18.4%)	83 (36.6%)	14 (40%)	44 (20.5%)	207 (14.6%)
B	675 (35.7%)	105 (46.3%)	13 (37.1%)	86 (40%)	471 (33.3%)
C	372 (19.7%)	27 (11.9%)	4 (11.4%)	38 (17.7%)	303 (21.4%)
D	488 (25.8%)	12 (5.3%)	2 (5.7%)	46 (21.4%)	428 (30.3%)
Median age at the last follow-up [IQR]	19.8 [18.0, 21.3]	12.2 [10.5, 14.4]	11.9 [10.6, 13.4]	20.3 [18.6, 22.5]	20.1 [18.4, 21.6]
Median age at seroconversion [IQR]	7.1 [4.0, 10.5]	5.0 [2.9, 7.9]	-	9.5 [6.6, 13.6]	-
Median age at diagnosis [IQR]	12.6 [11.2, 15.0]	12.7 [11.2, 14.9]	12.4 [11.3, 16.1]	-	-

433 **Table: Description of the study subjects**434 Description of the cohort of subjects followed beyond age 10 at least until age 18 or diagnosed with type 1 diabetes between age 10
435 and 18. *Note that 19/1883 (1%) of subjects are not included in the HLA groups due to indeterminant typing results.

436

437
438

439 **Figure legends**

440 **Figure 1: Follow-up times of the study subjects** Follow-up time for the 1890 subjects in the
441 cohort. Each horizontal line represents the timeline for one subject, where the start of the line is
442 the time when the subject was started to be followed and the end of the line is the time when the
443 subject was diagnosed with type 1 diabetes (red and orange lines) or when the subject was lost to
444 follow-up (dark and light blue lines).

445

446 **Figure 2: Number of all subjects, newly seroconverted, islet autoantibody positive, and**
447 **those diagnosed with type 1 diabetes**

448 (A) Number of subjects who had at least one visit between age of 10 and 18 years, followed
449 through each age range for each study site. (B) Number of subjects newly seroconverted at each
450 age range (islet autoantibody incidence). (C) Number of subjects with any islet autoantibody at
451 each age range (islet autoantibody prevalence). (D) Number of subjects diagnosed with type 1
452 diabetes at each age. (A-D) The number of subjects at each age (or age range) includes subjects
453 within a window from 6 months before to 6 months after the specified age (or age range),
454 respectively.

455

456 **Figure 3: Median time from seroconversion to type 1 diabetes**

457 The median time from seroconversion to diagnosis of type 1 diabetes by age at diagnosis in the
458 227 subjects followed in the complete cohort. Pearson's correlation 0.88 (95% CI 0.50-0.97,
459 $p=0.002$). The horizontal green line represents the median, the box extends from the Q1 to Q3

460 quartile, and the upper/lower whisker extends to the last datum less/greater than $Q3 + 1.5 * IQR /$
461 $Q3 - 1.5 * IQR$. Open circles beyond the whiskers represent outliers.

462

463 **Figure 4: Comparative sensitivity and positive predictive value (PPV) of screening for any**
464 **islet autoantibody**

465 Comparative sensitivity (A) and PPV (B) from screening any islet autoantibody at single ages
466 (diagonal numbers highlighted within black squares) and at all combinations of two ages

467 between 10 and 17 years for risk of type 1 diabetes in subjects followed beyond age 10. The

468 highest comparative sensitivity indicates the optimum screening age (at age 10: 63%; 95% CI

469 56-71) or age pair (at ages 10 and 14: 72%; 95% CI 65-78) to detect the maximum number of

470 subjects developing type 1 diabetes during follow-up, which were also assessed by direct

471 observation. The PPV at single age or age pair indicates the likelihood that autoantibody positive

472 subjects develop type 1 diabetes during the follow-up. Observed sensitivity and PPV are not

473 shown in these figures but are noted both in the Summary and the Results sections.

474