Two-Age Islet Autoantibody Screening for Childhood Type 1 Diabetes

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Abstract

**Background:** Early prediction of childhood type 1 diabetes reduces ketoacidosis at diagnosis and provides opportunities for disease prevention. However, only highly efficient approaches are likely to succeed in public health settings. We sought to identify efficient strategies for initial islet autoantibody screening in children under 15 years of age.

**Methods:** We harmonized data from five prospective cohorts from Finland (DIPP), Germany (BABYDIAB), Sweden (DiPiS) and the USA (DAISY and DEW-IT) into the Type 1 Diabetes Intelligence (T1DI) cohort, comprising 24,662 high risk children enrolled early in life and followed for islet autoantibodies and diabetes until 15 years or T1D onset, whichever occurred first. Main outcomes were sensitivity and predictive value of detected islet autoantibodies, tested at one or two fixed ages.

**Findings:** Type 1 diabetes developed by age 15 in 672 children. Optimal screening ages for two measurements were 2 and 6 years, yielding sensitivity of 82% and positive predictive value of 79% for diabetes by age 15. Autoantibody positivity at each test age was highly predictive of diagnosis in the subsequent 2-5.99 or 6-15 age intervals, respectively. Autoantibodies usually appeared early in life even in those with onsets nearer to age 15. Including children with even a single autoantibody at initial screening was essential for high sensitivity. Comparative sensitivity at ages 2 and 6 did not differ between higher and lower risk HLA groups but was greatest in Finland (DIPP) at ages 2 and 6, while in Colorado (DAISY) ages 2 and 9 performed best.

**Interpretation:** Initial screening for islet autoantibodies at two ages (2 and 6 years) is sensitive and efficient for public health translation but may require adjustment by country based on population-specific disease characteristics.

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Research in context

Evidence before this study
Most childhood type 1 diabetes (T1D) cases appear in those with high HLA DR-DQ genetic risk, but about one quarter of cases have lower HLA risk. Islet autoantibodies (IAb) are known to precede diagnosis and can reveal those at greatest future risk of T1D. Knowing IAb status in advance can prevent most DKA at onset, and immunotherapy applied in IAb-positive individuals was recently shown to significantly delay onset. Multiple IAb mark the greatest risk as do IAb appearing in early childhood. However, autoimmunity may evolve over time, and those initially with single IAb or with IAb appearing later in childhood, can also progress to clinical disease. Most large studies to date have followed children at high HLA or familial risk via frequent IAb testing throughout childhood. While sensitive and specific, these approaches are not cost-effective for population-wide T1D prediction.

Added value of this study
Our results show that testing at only two ages is sufficient to detect a large majority of cases occurring by age 15 years. We found that including single IAb positive children provided a key part of this sensitivity, especially at young ages. Our results, although primarily from children prescreened for elevated genetic risk, suggest that this strategy might apply even in those at lower HLA risk. Another key finding was that two-age IAb testing may have different optimal ages in different geographical regions.

Implications of all the available evidence
A sensitive, efficient initial testing strategy implies that population-wide screening for future T1D is practical to make disease prediction and prevention accessible to most childhood cases.
Introduction

Islet autoantibodies (IAb) are useful biomarkers of future type 1 diabetes (T1D), although the time from the appearance of autoimmunity to clinical diagnosis is highly variable. In young children, many studies have shown that most diabetic ketoacidosis (DKA) at T1D onset can be prevented by IAb surveillance, with subsequent patient education and monitoring of deteriorating glucose metabolism\(^1,2\). Prevention therapy to delay T1D clinical onset in those with IAb has also recently been successful\(^3\). Prospective study of children at preclinical stages of T1D is also essential to refine markers of progression, and to better understand disease mechanisms.

Both genetic screening and IAb surveillance have become more accurate and less expensive\(^4,5\) and have been shown to be sensitive and specific to predict T1D\(^6,7\). However, substantial challenges must be met before public health adoption of population-wide pediatric T1D prediction. Both to prevent the most severe cases of DKA, and to provide opportunity for prevention therapy to delay the onset of clinical diabetes, IAb detection must occur early enough in life to precede the highest incidence period between ages 2 and 15 years. Childhood T1D is a severe disease, but its incidence of about 1/300 children is low enough that decreasing DKA, delaying onset of hyperglycemia, and improving post-onset disease course, together yield only moderate aggregate medical cost savings. To achieve commensurate low costs for a prediction program requires highly efficient strategies with limited testings\(^8\). Prescreening using recent advances in genetic risk assessment can greatly improve efficiency\(^4\), but wise initial IAb testing also plays a key role. Of course, fewer tests inevitably bring sensitivity losses, and it is essential to optimize initial screening strategies to maximize sensitivity. After the screening we describe is completed, subsequent follow-up autoantibody surveillance testing with greater specificity may then lead to glycemic monitoring, education on symptoms to prevent DKA, and consideration of prevention therapy.
The Type 1 Diabetes Intelligence (T1DI) Study\textsuperscript{9} offers a uniquely large and harmonized dataset combining multiple birth cohort studies which tested children frequently through adolescence. Using T1DI, we sought to identify optimum pediatric islet autoantibody testing strategies to efficiently reveal future T1D risk, ultimately for translation to public health and medical care.

**Research Design and Methods**

**Study Cohort.** The T1DI study cohort\textsuperscript{9} incorporated participants from five prospective longitudinal cohorts: the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study\textsuperscript{10}, the Swedish Diabetes Prediction in Skåne Study (DiPiS)\textsuperscript{11}, the Diabetes Autoimmunity Study in the Young (DAISY) from Colorado, USA\textsuperscript{12}, the Diabetes Evaluation in Washington (DEW-IT) from Washington State, USA\textsuperscript{13}, and BABYDIAB from Germany\textsuperscript{14}. Local Institutional Review Board approval, parental informed consent, and child assent where relevant, were obtained for all study participants. A total of 24,662 subjects were followed from early childhood (DIPP n=11,652 (47\% of cohort), DIPIS n=4,359 (18\%), DAISY n=2,539 (10\%), DEW-IT n=3,748 (15\%), BABYDIAB n=2364 (10\%)) and of these 6,722 total (3,605 females) were followed through age 15 years or until T1D. This included 6,050 children who did not develop T1D, and 672 diagnosed with T1D by age 15 (Supplemental Figure S1). A median of 18 [interquartile range (IQR) 14-24] samples per participant were analyzed for IAb. The median age at first test was 4·2 months (2·4-9·6), the median follow-up time was 15·4 years (15·0-17·5) and the median age for first IAb appearance in was 4·5 years (2·0-8·6). Islet autoantibodies against glutamic acid decarboxylase, insulinoma antigen-2 and insulin were measured in serum or plasma using workshop-validated methods as described in each respective study\textsuperscript{9-14}. Zinc transporter 8 (ZnT8) antibodies were not systematically measured in all samples and were not included in this analysis. All DIPP, DiPiS and DEW-IT, and some DAISY subjects, underwent HLA screening.
before enrollment, while all BABYDIAB and some DAISY children were enrolled based on having a first degree relative (FDR) with T1D. Overall, approximately 72% of the cohort did not have a first degree relative with T1D. Because of the FDR enrollment, and because low resolution HLA genotyping was used in some centers, the resultant combined cohort, while weighted towards HLA genotypes conferring high T1D risk, also contained some individuals with lower HLA risk. To analyze this broad variation in underlying risk, T1DI has defined four HLA DR-DQ risk groups\(^9\) based on published odds ratios for T1D (detailed in Supplemental Table 1A and 1B). In summary, 1,163 children were in Group A (very high risk), 3,678 in Group B (high risk), 951 in Group C (slightly elevated risk), 911 in Group D (average to very low risk), and 19 were unassignable.

**Screening Test.** At each screening timepoint, serum was tested for the three islet autoantibodies as previously described\(^9\). To model the use of IAb at a specific age, we considered subjects who had at least one sample drawn within a window from 6 months before to 6 months after the specified test age. Within each annual age window, a participant was designated as testing positive, negative, or having no result available. We analyzed two screening endpoints: either requiring the presence of more than one of these three islet autoantibodies, deemed “Multiple IAb” or simply requiring one autoantibody or more to be positive, called “Any IAb”. We considered tests at yearly ages (1 to 14 years) to identify screening ages with the best performance. To maximize testing efficiency, we considered screening at only one or two ages. Due to earlier diagnosis, the number of subjects followed at older ages was less than those followed earlier. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used as time-dependent metrics to evaluate screening at each age\(^15\). Each subject was classified as a case if diagnosed in the specified age period, or otherwise as a control.
regardless of their disease status after age 15 years. Since compliance with testing varied with age, a meaningful comparison of various age combinations required the calculation of cumulative sensitivity\(^{15}\) where cases with missing tests were included in the denominator of sensitivity calculations. These sensitivities are herein termed “comparative sensitivity”.

However, once an optimum strategy was chosen, its true sensitivity among children completing the testing and observation was also calculated and referred to as the “observed sensitivity”.

**Statistical Analyses.** Inverse probability censoring weighting (IPCW) was applied to data from all 24,662 subjects (see Supplemental Figure S2) to account for non-random loss to follow-up\(^{16}\). Each 95% confidence interval was computed as mean±1.96*SD from 1000 total runs using a bootstrap resampling technique selecting a random sample of subjects with replacement. Two-sided t-tests were used for comparisons. The bootstrap method was also used to objectively identify the best screening age pairs. Using a 10,000-run bootstrap set for each screening age pair, we computed sensitivity and PPV. The best pair was defined as having the minimum distance \((1\text{-sensitivity})^2 + (1\text{-PPV})^2\) to the top-left corner of a sensitivity versus 1-PPV plot, an approach analogous to the Youden index in standard ROC analysis\(^{17}\).

**Results**

Screening at two ages performs better than at a single age, and “Any IAb” had greater comparative sensitivity but lower positive predictive value than “Multiple IAb”. The comparative sensitivities and PPVs of requiring “Multiple IAb” and “Any IAb” are shown in Figure 1 for all ages from 1 to 14 years and for all two-age combinations within this range. Corresponding specificities and negative predictive values for these age combinations are shown in Supplemental Figures S3 and S4. Not surprisingly, a more extensive two-age strategy was far
more sensitive than screening at only one age, with the same positive predictive value at the sensitivity maxima. This was true for both the “Multiple IAb” (51% vs 33% comparative sensitivity) and “Any IAb” (66% vs 46%). For two-age screening, the comparative sensitivity of 66% (95% CI 63%, 69%) for “any IAb” was relatively high, and came with a PPV of 54% (51%, 58%). This contrasts with the “Multiple IAb” strategy, whose lower comparative sensitivity of 51% (47%, 54%) came with a higher PPV of 74% (69%, 78%). This tradeoff is expected and is often observed when comparing a lower stringency test to one of higher stringency. Our analyses indicated the age optimum for a single screening was 4 years while for a two-age screening there appeared to be a broad optimum sensitivity with first screening at ages 2 to 4 years and second screening at ages 6 to 9 years (Figure 1). PPVs were best at the youngest ages within these ranges, and choosing the youngest screening ages within the optimum range also enabled the screening to be undertaken earlier in life to precede more T1D onsets. Further confirmation of optimum two-age screening pairs used bootstrap internal replication and an approach using plots similar to Receiver Operating Characteristic curves (Figure 2A). These analyses clearly identified 2 and 6 years as the best ages for two-age screening in our cohort (Figure 2B).

Comparative Sensitivity of the screening did not change based on HLA risk of the underlying population. We asked whether the identified screening optima performed differently for four differing HLA DR-DQ risk levels for T1D (Supplemental Table S1)\textsuperscript{11}. The higher risk Groups A+B were combined (n=4,841) and were compared to the combined lower risk Groups C+D (n=1,862). We found that differences in optimum screening ages between these two groups were not significant. For example, screening at ages 2 and 6 years for any IAb had comparative sensitivity to detect 67% (95% CI 64%-70%) of T1D cases for HLA Groups A+B versus 64%
(57%-71%) for HLA Groups C+D (Figure 3A and Supplemental Figure S5). PPV was greater for HLA Groups A+B at 59% (54%-63%) than for HLA Groups C+D at 45% (38%-53%).

Prediction performance differed by country. To test whether results from the combined T1DI cohort apply to different populations, we compared results between the Finnish DIPP study and the Colorado DAISY study, the two largest T1DI sub-cohorts from different continents. We used the “Any IAb” strategy and calculated the comparative sensitivity of two-age screening at varying ages. In DIPP participants comparative sensitivity was highest (74%, 95% CI 71%-78%) at screening ages 2 and 6 years with a 57% PPV (Figure 3B and Supplemental Figure S6). At ages 2 and 6, DAISY data showed lower comparative sensitivity (58%, 50%-67%) at a similar 58% PPV. Interestingly, for DAISY, the “Any IAb” strategy appeared to perform better at ages 2 and 9 years, with sensitivity of 66% (59%-74%) and a 54% PPV.

Observed sensitivity of the optimum screening strategy was very high. To compare performance of various two-age screening pairs in a dataset with variable numbers of subjects tested at each specified age, “comparative” sensitivities (using the cumulative sensitivity method\textsuperscript{15}) were calculated by a formula where cases with missing tests were included in the denominator even though the testing strategy could not be applied to those cases. This was necessary to allow comparison of screening results from all age pairs (Figures 1-3). However, it led to lower sensitivity estimates than the directly “observed sensitivity” which considered only subjects actually tested at the specified ages. Therefore, the optimum strategy identified by comparative methods was then assessed by direct observation. We first displayed observed risk by IAb result (IAb negative, not tested in age window, one IAb present or multiple IAb present). A single IAb at age 2 indicated a 31% four-year risk of developing T1D by age 5-99, while multiple IAb at age 2 carried a 55% four-year risk (Figure 4A). A single IAb at age 6 conferred, over the next
nine years, an overall risk of 38% if the IAb test at age 2 was negative or missing, but an overall risk of 73% if the age 2 testing detected any IAb. Multiple IAb at age 6 years indicated an overall risk of 83% by age 15 regardless of IAb status at age 2 years (Figure 4B). Finally, the observed sensitivity of various screening strategies and T1D onset intervals is summarized in Figure 4C for children actually tested at the indicated ages and followed through age 15. Each screening test (at age 2 or age 6) was highly sensitive for T1D onsets in the time interval following the test, with sensitivity of 82% (79-86%) and predictive value of 79% (75%-80%) of the combined age 2 plus 6 screening to detect T1D onsets occurring between ages 2 and 15.

Progression from IAb to T1D was slower for onset at older ages. We sought to understand why early testing (ages 2 and 6) was so efficient at detecting most children developing T1D much later, up to age 15. Analysis of the T1DI dataset indicated that as age at T1D diagnosis increases, the average time interval between IAb seroconversion and T1D diagnosis increases dramatically (P<0.001) (Supplemental Figure S7, blue symbols). Autoantibodies often appeared early in life even in those progressing slower to late childhood onsets. This effect is present throughout the peak years of T1D incidence as indicated by annual incident cases (Supplemental Figure S7, maroon symbols).

Discussion

Early detection of islet autoantibodies in children has been widely shown to prevent DKA at diagnosis\(^1,2\) and also provides an opportunity to apply prevention therapies\(^3\). For this reason, islet autoantibody screening strategies have been extensively studied in pediatric populations\(^18,19\). However, the relatively low prevalence of T1D makes it difficult to accomplish pediatric screening at a cost acceptable for public health translation\(^8,20\). The combined T1DI cohort has a
large sample size, multiple measurements per individual, and long follow-up to allow comprehensive evaluation of multiple testing strategies. We found that screening at only two ages in childhood can identify a large majority of children who will develop T1D by age 15. Fewer tests means lower screening costs and greater accessibility.

Many studies focus on multiple IAb positive children as a primary target of detection. However, a major goal of screening is to be sensitive enough to not miss potential cases. The specificity and predictive value then rise during follow-up confirmation and further testing. Of participants developing only one persistent IAb in the T1DI cohort, 80% had the next available sample drawn within a year, and in two-thirds of those the IAb was confirmed and persistent. High confirmation rates among single IAb children have also been described in other studies\textsuperscript{18}. Specificity might also be increased by higher autoantibody titers, higher affinities, or disease-specific epitopes\textsuperscript{21}, and of course monitoring for glycemia and early symptoms. The number of pediatric subjects in whom follow-up testing is needed is small, and thus not a substantial part of population-wide prediction costs. For example, the German FR1DA study found the prevalence of multiple IAb to be 0·31% of all 2 to 5-year olds\textsuperscript{19}. Before that, a combination of other birth cohort studies found that multiple IAb represented 585/1059 (55%) of those with any IAb\textsuperscript{6}. This implies that the overall prevalence of any IAb is estimated at 0·31% ÷ 55% = 0·56%, of which nearly half (about 1 in 400 children) have a single IAb. In our cohort, even a single IAb at age 2 marked a high risk to develop future T1D. Of children with a single IAb at age 2, two-thirds developed T1D by age 15 (based on Figure 4). Of those with a single islet antibody first appearing at age 6, more than one-third had developed T1D by age 15, a substantial risk for a single autoantibody first appearing in a school-age child. Taken together, these results are consistent with our 79% PPV for T1D by age 15 for “Any IAb” in the two-age screening
strategy. We believe this is an acceptably high PPV for initial pediatric screening, especially when complemented by timely follow-up evaluation.

Screening at young ages carries some advantages. IAb appearing earlier have long been known to indicate a higher T1D risk\textsuperscript{22,23}, and in the T1DI cohort the youngest age combinations indeed had the highest PPVs. Early screening at age 2 increases the number of children found prior to diagnosis, where DKA can be prevented and T1D prevention therapies offered. Likewise, the second test at age 6 occurs at the end of the largest wave of seroconversions\textsuperscript{24} capturing most IAb positive children early enough to offer prevention therapy. Prior studies suggest that parental anxiety levels are usually not increased when a child is found to be at increased genetic risk\textsuperscript{25}. Parental anxiety does increase when children are found to be IAb positive, but then decreases back towards baseline over time\textsuperscript{26}.

Importantly, we observed similar screening sensitivity across a spectrum of high and moderate HLA risk, implying that the pattern of IAb development may be sufficiently similar to be amenable to a uniform screening protocol under a variety of genetic risk scenarios\textsuperscript{27}. While any genetic prescreening results in loss of some future cases, steadily improving genetic methods (e.g. genetic risk scores) have reduced these losses, for example selecting the 21\% of the pediatric population containing 89\% of the future cases\textsuperscript{4}. While we did not perform a formal cost-benefit analysis, genetic testing currently costs less than one-third the cost of a three IAb panel\textsuperscript{28}. This suggests that a genetic pretest followed by screening of children with the 21\% highest risk twice during childhood for IAb might detect most (but not all) future cases at a lower cost than a single cross-sectional IAb screening of all children.
Our study has some limitations. The studies comprising our combined dataset had different risk criteria and sampling schedules. Compliance with these schedules also varied, although an average of 18 samplings per child implies good coverage of the surveillance interval in most cases. We did not consider zinc transporter 8 autoantibodies, a test previously noted to provide a small increase in the number of multiple antibody children identified in follow-up but not to add significantly to identifying single autoantibody positivity. Our combined cohort included approximately 28% first degree relatives. Relatives are known to have on average a younger age at autoantibody appearance, which could make the 2-age screening strategy appear to perform better. Further, in our cohort first degree relatives are a significantly greater proportion of the HLA C+D group than the A+B group which may affect the performance of the 2-age screening when comparing those groups. Our results have not yet been validated in a separate cohort, because we are not aware of any cohort covering similar testing ages and frequency of follow-up. However, the TEDDY Consortium covering very similar populations of entirely different children, will be an ideal for validation in the coming years. Ultimately, replication must occur in general populations unselected for family history of type 1 diabetes (with or without genetic preselection) and especially in populations with greater geographic and ancestral diversity.

Public health implementation in different countries must take into account varying genetic features as well as different environmental exposures. The latter may elicit different subtypes of T1D, a possible explanation for the different optimal screening ages seen in the Finnish DIPP Study as compared to the Colorado DAISY Study. Screening ages and strategies must also fit in with health care systems which vary due to local/regional politics and resources, differing glycemic monitoring during the presymptomatic period and different treatment practices at onset. IAb assay quality must be reasonably high, as in the current dataset where all
labs took part in periodic international proficiency testing. Regions that implement efficient web or cloud-based coordination of testing, reporting, and treatment will also benefit from improved cost efficiency.

**Conclusion**

We demonstrate that screening at just two early ages detected most future childhood type 1 diabetes cases and may be practical for public health implementation. When used after a genetic prescreening, most future cases would be detected, all at a net investment of less than one IAb measurement per child. Following children with any IAb rather than just multiple IAb increases case detection with acceptable predictive value. The screening strategy appears to work in subjects with varied HLA background risk, but optimum screening ages differ between countries.

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the discussion, editing and review, and all authors approved the final manuscript. M.L., M.R., A-G.Z., W.H., J.T., V.A. and R.V. verified the underlying data from their respective sites, and M.G. verified all study data and takes responsibility for the accuracy of the data analysis.

**Data Sharing:** The data supporting these study findings are available through the T1DI Consortium upon reasonable request to the corresponding author. The data are not publicly available due to privacy regulations.

**Abbreviations:** IA: islet autoimmunity; IAb: Islet autoantibody; GADA: glutamic acid decarboxylase antibody; IA-2A: insulinoma antigen-2 antibody; IAA: insulin autoantibody; ZnT8A: zinc transporter 8 antibody, HLA: human leukocyte antigen; T1DI Study Group: Type 1 Diabetes Intelligence Study Group.

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