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On the road to universal screening for risk of type 1 diabetes

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In this issue of *The Lancet Diabetes & Endocrinology*, Mohamed Ghalwash and colleagues[1] sought to determine the optimal age or ages for islet-autoantibody screening to predict the development of clinical type 1 diabetes by 15 years of age. The authors combined five birth cohorts (from the DIPP cohort in Finland, DiPiS cohort in Sweden, DAISY cohort in Colorado, USA, DEW-IT cohort in Washington, USA, and BABYDIAB cohort in Germany) with a total of approximately 25 000 children at risk for type 1 diabetes. The analysis focused on almost 7000 of these participants, who had been followed up to age 15 years or, in about 10% of the cases, developed clinical type 1 diabetes. Data from the remaining children, with shorter follow-up, were used to mitigate the potential bias caused by non-random loss of follow-up, by applying inverse probability censoring weighting, a method that accounts for right-censored outcomes. The relative homogeneity of the study samples and available data allowed harmonisation of the five studies, and the resulting large size of the combined dataset is one of the strengths of the analysis. Autoantibodies to insulin, GAD65, and IA-2 were tested at several, varying timepoints.

The major novel finding in this study is that testing for islet autoantibodies at 2 years and 6 years of age had the highest sensitivity (82%) and positive predictive value (79%) for diabetes by age 15 years. That is, 82% of the individuals who developed type 1 diabetes by age 15 years were identified by the autoantibody screening strategy proposed by the authors, and 79% of the participants identified as being autoantibody positive ultimately developed the disease. This performance seems acceptable for a screening strategy, in which the individuals ascertained would receive education, additional testing to refine the prediction, and monitoring for progression to clinical disease.

The study found additional results that are consistent with previous literature, including contributions by the authors. For instance, multiple autoantibody positivity had lower sensitivity but higher positive predictive value, consistent with the known higher risk of progression to clinical type 1 diabetes,[2,3] compared with positivity for a single autoantibody. Screening at two ages performed better than at a single age, which is not surprising given that autoantibodies can appear in serum throughout childhood.[4] After islet autoimmunity is first identified, the rate of progression to clinical type 1 diabetes varies depending on genetics, autoantibody characteristics (eg, number, type, and titre), metabolic measures (eg, BMI), and demographic factors (eg, age, race and ethnicity, and sex),[3,5,6] in line with the study observation of variable progression even in the children who seroconverted early in

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life. The differences in prediction performance between the DIPP and DAISY study might be secondary to geographical diversity in the genetic and environmental factors for islet autoimmunity and type 1 diabetes.

Positive predictive value (ie, the likelihood that a participant identified as being autoantibody positive will develop type 1 diabetes) was greater for the high-risk HLA group, probably because of higher disease prevalence in this group[7] than in participants with low-risk HLA. Interestingly, the sensitivity (or, in other words, the ability of the screening strategy to identify correctly those who will develop clinical type 1 diabetes) was not different between the low-risk and high-risk HLA groups. However, genetic homogeneity of the study sample and incomplete genetic data might have influenced this result.

This study is timely because recent successes in preventing type 1 diabetes[8] highlight the need to identify the best candidates for intervention.[9] Outstanding questions for future research include replication in an independent dataset, applicability to the general population, further refinement of the model, and implementation of the strategy. The authors point out at the scarcity of cohorts suitable for replication and anticipate being able to use the TEDDY study when its 15-year age endpoint is reached. It remains to be seen whether Ghalwash and colleagues' strategy could work in the general population because all the participants in the combined dataset had genetic risk factors for the disease or a relative with type 1 diabetes, in whom performance is expected to be higher. Furthermore, most participants were of northern European ancestry and, given the known differences in type 1 diabetes epidemiology and pathogenesis,[10] other ancestries must be studied. Similarly, it is still unknown whether the screening strategy can be applied in individuals older than 15 years, in whom typically slower progression of preclinical type 1 diabetes is seen. Refinements of the screening tool might include adding ZnT8 autoantibodies, considering differential prediction by autoantibody type or titres, or leveraging genetic information, possibly in the form of genetic risk scores, as a first step. These improvements, along with advanced statistical methods, should provide more information about the best ages to test, and increase the model's performance. In addition, as suggested by differences found in the analysis between DIPP and DAISY, the model might require adaptation to local factors that affect the progression and prevalence of type 1 diabetes. Finally, important aspects, such as screening cost, global access, acceptability, and follow-up support will need to be addressed for this strategy to be a viable public health option. In summary, this paper constitutes an important contribution to the literature and generates several additional research questions for the future.

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