Clinical Characteristics of Children Diagnosed With Type 1 Diabetes Through Intensive Screening and Follow-Up

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OBJECTIVE — The objective of this study was to determine whether earlier diagnosis of diabetes in prospectively followed autoantibody-positive children lowered onset morbidity and improved the clinical course after diagnosis.

RESEARCH DESIGN AND METHODS — The Diabetes Autoimmunity Study in the Young (DAISY) follows genetically at-risk children for the development of diabetes. Increased genetic risk is identified by family history of type 1 diabetes or expression of diabetes-associated HLA genotypes. Of the 2,140 prospectively followed children, 112 have developed islet autoantibodies and 30 have progressed to diabetes. Diabetes onset characteristics and early clinical course of these 30 children followed to diabetes were compared with those of 101 age- and sex-matched children concurrently diagnosed with diabetes in the community.

RESULTS — Pre-diabetic children followed to diabetes were less often hospitalized than the community cases (3.3 vs. 44%; $P < 0.0001$). They had a lower mean HbA_{1c} at onset (7.2 vs. 10.9%; $P < 0.0001$) and 1 month after diagnosis (6.9 vs. 8.6%; $P < 0.0001$) but not after 6 months of diabetes. The mean insulin dose was lower in the DAISY group at 1 (0.30 vs. 0.51 $U \cdot kg^{-1} \cdot day^{-1}$; $P = 0.003$), 6 (0.37 vs. 0.58; $P = 0.001$), and 12 months (0.57 vs. 0.72; $P = 0.03$). There was no difference in growth parameters between the two groups. Comparisons limited to children with a family history of type 1 diabetes in both groups showed a similar pattern.

CONCLUSIONS — Childhood type 1 diabetes diagnosed through a screening and follow-up program has a less severe onset and a milder clinical course in the first year after diagnosis.

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Type 1 diabetes affects ~15–30 million people globally and 1.4 million in the U.S. (1,2). The incidence is increasing by 3–5% per year (3,4), especially among young children (5–9). Type 1 diabetes is responsible for significant morbidity, premature mortality (10), and financial burden (11). The disease usually is preceded by a preclinical period lasting months to years. Pre-diabetes can often be detected by the presence of autoantibodies to islet antigens such as GAD65, insulin, and IA-2 that are highly predictive of type 1 diabetes risk in children with (12) and without (13) a first-degree type 1 diabetic relative.

In the absence of effective prevention, screening for pre-diabetes is currently not recommended outside of research studies. To date, interventions applied after the development of islet autoantibodies have been unsuccessful in slowing progression to diabetes (14,15). Several ongoing cohort studies (16–19) follow high-risk children from birth to determine environmental triggers of type 1 diabetes. Interventions based on avoidance of these triggers before the onset of autoimmunity could be effective in preventing type 1 diabetes.

One of these projects, Diabetes Autoimmunity Study in the Young (DAISY) (16,19), intensively follows two groups of children at increased risk for the development of diabetes: young first-degree relatives and infants identified from population screening as carrying HLA-DR,DQ genotypes associated with type 1 diabetes. Here, we report clinical characteristics of children who developed diabetes while participating in DAISY screening and follow-up.

Children diagnosed with diabetes through the DAISY study are expected to present earlier in the disease process. However, it is unknown if earlier diagnosis through screening for pre-diabetes and follow-up confers any benefit to the participating children. The objective of this report was to determine whether participation in the DAISY study significantly decreased the incidence of onset hospitalization and growth delay and improved the HbA_{1c} and insulin dose through the first year after diagnosis of diabetes compared with matched contemporary community cases.

RESEARCH DESIGN AND METHODS

— Since 1994, DAISY has enrolled and prospectively followed two

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Abbreviations: DAISY, Diabetes Autoimmunity Study in the Young; DKA, diabetic ketoacidosis; IAA, insulin autoantibody.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

groups of children: young first-degree relatives of patients with type 1 diabetes (sibling or offspring cohort) and newborns from the general population expressing HLA-DR,DQ genotypes associated with type 1 diabetes (newborn cohort). The latter were identified as neonates born at St. Joseph's Hospital in Denver, Colorado, by screening cord blood. The newborn population was representative of the general population of the Denver metropolitan area. We did not recruit families in which parents had difficulty understanding English or whose newborn was in very poor health due to extreme prematurity, severe congenital malformation, or disease, as assessed by hospital personnel. Eighty-six percent of the families approached gave informed consent to the genetic screening. HLA screening has been completed on >30,000 newborns; the details of the newborn screening have been published elsewhere (16). Based on their HLA genotype, newborns were categorized into three risk groups determined by the odds of developing type 1 diabetes by the age of 20 years: high (the odds of type 1 diabetes being 1:16); moderate (1:75 in non-Hispanic whites or 1:230 in Hispanics); or low (<1:300). All newborns found to be at high risk and a sample of those found to be at moderate risk were asked to participate in the follow-up.

In addition to the HLA-screened population, children younger than age 4 years were recruited from families with type 1 diabetes using The Barbara Davis Center for Childhood Diabetes in Denver, Colorado, other diabetes care clinics, the Colorado type 1 diabetes registry, and newspaper publicity. The study population consists of 1,228 HLA-screened children without a family history of type 1 diabetes and 929 children with a first-degree relative (parent or sibling) with type 1 diabetes.

Follow-up visits consisted of height and weight determination, serum obtained for autoantibodies to GAD65, insulin, and IA-2, and questionnaires to determine specific environmental exposures. Children were followed at 9, 15, and 24 months of age and then annually. If a child was found to be autoantibody positive, the family was notified of the result and instructed in symptoms of hyperglycemia. They were then followed in the study clinic every 3–6 months for islet autoantibodies, HbA_{1c}, and random blood glucose obtained on a glucometer. Referral for evaluation by a pediatric endocrinologist was initiated if the child was symptomatic, if the random blood glucose was elevated (>6 mmol/l), or if the HbA_{1c} increased toward the upper limit of the normal range of the DCA2000 assay (6.4%). Insulin therapy was initiated for symptomatic hyperglycemia and/or for blood glucose levels that were consistently elevated, meeting the American Diabetes Association criteria for diagnosis of diabetes (20). The 30 children diagnosed with type 1 diabetes through the DAISY study are the subjects for this study. Twenty-seven of the 30 children diagnosed with diabetes had autoantibodies measured within 1 year of diagnosis. Of these 27, 5 (18.5%) were positive for one autoantibody, 14 (51.8%) were positive for two autoantibodies, and 8 (29.6%) were positive for three autoantibodies at the last visit before diagnosis of diabetes. Insulin autoantibody (IAA) was detected in 22 (81.5%), IA-2 in 18 (66.7%), and GAA in 17 (63.0%) participants. Two individuals had negative autoantibodies at 0.75 and 1.3 years of age, were lost to follow-up, and were then diagnosed with type 1 diabetes at 5.7 and 7.7 years. One individual had been enrolled but autoantibodies were not obtained before diagnosis.

A comparison group was retrospectively ascertained from among all children diagnosed with type 1 diabetes and referred to the Barbara Davis Center for clinical care at the onset of diabetes from January 1999 to November 2002. The Barbara Davis Center serves as one of two referral centers for the care of children with type 1 diabetes in the Rocky Mountain region. Children considered for comparison were limited to a similar geographic distribution as those that were enrolled in DAISY. They all lived in major metropolitan areas within the referral base of the Barbara Davis Center. They also had access to care in a tertiary care center familiar with the care of children with type 1 diabetes and diabetic ketoacidosis (DKA). Children with significant comorbidities that may affect growth (Turner's syndrome, Down's syndrome, and known celiac disease) were excluded. There were 301 children meeting the above criteria, 111 of those had islet autoantibodies (to GAD65, IA-2, or insulin) measured within 10 days after first insulin injection, and 101 of these children were positive for at least one autoantibody. Thirty-four (33.7%) were positive for all three, 42 (41.6%) were positive for two autoantibodies, and 25 (24.8%) were positive for one autoantibody. IA-2 autoantibody was the most frequently detected with 81 (80.2%) children positive; IAA was positive in 68 (67.3%), and GAA was positive in 60 (59.4%).

Comparisons between DAISY and community children

The groups were compared for onset HbA_{1c} and hospitalization. At our center, most families receive outpatient initial diabetic teaching and management for 2–3 days immediately after diagnosis. Therefore, hospitalization at onset of diabetes is almost always due to DKA or significant comorbidity (21). Laboratory parameters for those children hospitalized were obtained where available. For the purposes of this report, DKA was defined as venous pH ≤7.3 and/or serum bicarbonate level ≤15 mEq/dl, glucose level >14 mmol/l, and the presence of urine or serum ketones. The growth parameters (height, weight, and BMI) at onset were standardized to 2000 Centers for Disease Control and Prevention growth charts and reported as *z* scores to allow for comparison of different ages and sexes.

HbA_{1c} and insulin dose through the first year of diabetes were also compared. Insulin dose was converted to $U \cdot kg^{-1} \cdot day^{-1}$. Insulin doses were compared at 1, 6, and 12 months after diagnosis. The first comparison was performed at 1 month after diagnosis to account for the affect of prolonged hyperglycemia on insulin dose and to allow for a steady-state insulin dose.

Measurement of autoantibodies

IAAs were determined by a micro-IAA assay with a sensitivity of 58%, a specificity of 99%, and an interassay coefficient of variation of 11%, as described previously (22). The combined GAD65 (GAA) and IA-2 autoantibody radioassay was performed in duplicate using methods previously described (23). The levels of the autoantibodies are expressed as an index = (sample cpm − negative control cpm)/(positive control cpm − negative control cpm). In the 1995 Immunology of Diabetes Society Workshop, the GAA assay gave an 82% sensitivity and a 99% specificity using sera from new-onset diabetic patients aged <30 years. The inter-

assay coefficient of variation was 6%. The IA-2 assay gave a 73% sensitivity and 100% specificity, and the interassay coefficient of variation was 10% (23). Based on 198 nondiabetic control subjects ages 0.4–67.5 years, the 99th percentile for IAA (0.01) and GAA (0.032) and the 99th percentile (single highest value) for IA-2 (0.049) were used as the cutoffs for positivity. All samples that were positive for IAA, GAA, or IA-2 and a random 10% of the remaining samples were retested in a blinded manner for confirmation.

Statistical analyses

Statistical analyses were performed using SAS 8.0. Student's *t* test was used for continuous variables. Analysis of variance was used for multiple comparisons with Bonferroni correction to determine the significance of specific pairwise comparisons. χ^2 analysis was used for categorical variables unless 20% of the cells had an expected value <5, in which case, Fisher's exact test was used. Results were considered statistically significant with an $\alpha < 0.05$.

RESULTS — To date, the DAISY study has screened >30,000 newborns at birth for HLA class II genotypes. Of these, 1,228 newborns with type 1 diabetes-associated genotypes were enrolled in prospective follow-up. They have been followed for a median of 4.0 years, and 25% have been followed for ≥6.4 years. We have followed 579 children who are offspring of type 1 diabetic patients, 333 who are siblings, and 17 children who are both a sibling and offspring. This cohort has been followed for a median of 5.3 years, and 25% have been followed for 8 years or more. Of the 2,157 enrolled in prospective follow-up, 112 have developed islet autoantibodies, and 30 have progressed to diabetes.

Baseline characteristics

The two groups were similar in terms of sex distribution: 53% female in the DAISY group vs. 45.5% in the control group (NS). The DAISY case subjects were slightly younger (5.9 vs. 7.7 years; $P = 0.01$). As expected given the selection criteria, the DAISY case subjects had a much higher proportion of children with a family history of type 1 diabetes compared with children diagnosed from the community (80 vs. 15%).

Onset hospitalization

The hospitalization rates differed dramatically between the two groups. One child (3.3%) in the DAISY group was hospitalized compared with 44 (44%) children in the community group ($P < 0.0001$). To see if this was an effect of the high proportion of individuals with a family history of diabetes in the DAISY group, the hospitalization rates were compared between children with a family history of diabetes in the DAISY group ($n = 24$) and community group ($n = 15$). One child in the DAISY group (1/24, 4.2%) was hospitalized compared with seven (7/15, 47%) in the community group with a family history of diabetes ($P < 0.01$).

Clinical data were available for 42 of 44 community children hospitalized at onset. For 35 children, pH and/or bicarbonate data were available to determine the presence of DKA. Twenty-nine (83%) of the 35 children had a pH <7.3 and/or bicarbonate <15 mEq/dl. pH data were available for 31 individuals; 9 had a pH ≤7.15. Intensive care was required for 33%. Average glucose at presentation was 35.2 ± 12.5 mmol/l, average bicarbonate 10.6 ± 5.9 mEq/dl, and average pH 7.21 ± 0.14. Individuals were hospitalized for a range of 1–3 days (mean 1.48 ± 0.65). Of the seven children in the community group with a family history of type 1 diabetes, clinical data were available for six. Five of the six individuals had DKA. pH ranged from 7.0 to 7.53 and bicarbonate from 3 to 19 mEq/dl.

Onset growth parameters

The DAISY and community children were compared for height, weight, and BMI at onset of diabetes. There was no difference between the two groups for these growth parameters at onset. DAISY and community children were similar in respect of the mean *z* scores for weight (−0.256 ± 1.29 vs. 0.069 ± 1.11), height (0.12 ± 0.83 vs. 0.41 ± 0.94), and BMI (−0.39 ± 1.28 vs. −0.16 ± 1.34). Similarly, in children with a family history of type 1 diabetes, there was no difference in the weight, height, or BMI *z* scores (data not shown).

HbA_{1c}

At diagnosis, HbA_{1c} was significantly lower in the DAISY children compared with the community children, with an average of 10.9% in the community group and 7.2% in the DAISY cohort ($P < 0.0001$). This difference persisted at 1 month. At 6 and 12 months, HbA_{1c} was equivalent in the two groups, as the community childrens' HbA_{1c} decreased with insulin therapy (DAISY 7.7%, community 7.9%; $P = 0.7$) (Fig. 1*A*).

A similar pattern was observed when comparing the children in each group with a family history of type 1 diabetes; the HbA_{1c} differed between the two groups at onset (DAISY 7.2% vs. community 10.3%; $P < 0.0001$) and at 1 month after diagnosis (DAISY 7.1% vs. community 9.5%; $P = 0.0001$). This difference disappeared by 6 months after diagnosis (DAISY 7.7% vs. community 7.5%; $P = 0.8$) (Fig. 1*B*).

Insulin dose

The children in the DAISY group had lower insulin doses at all time points analyzed. At 1 month after diagnosis, the DAISY children received an average of 0.30 U · kg^{-1} · day^{-1} compared with 0.51 U · kg^{-1} · day^{-1} in the community children ($P = 0.003$). In the DAISY group, the dose increased to 0.37 U · kg^{-1} · day^{-1} at 6 months and 0.57 U · kg^{-1} · day^{-1} at 12 months. In the community children, the dose increased to 0.58 U · kg^{-1} · day^{-1} at 6 months and 0.72 U · kg^{-1} · day^{-1} by 12 months after diagnosis. The differences between DAISY and community children remained significant at the 6- and 12-month time period ($P = 0.001$ at 6 months and 0.03 at 12 months) (Fig. 2*A*).

The same comparison was performed in the group with relatives with type 1 diabetes. At 1 and 6 months after diagnosis, the DAISY children had a lower insulin dose than community children. Insulin dose at 1 month was 0.30 U · kg^{-1} · day^{-1} in the DAISY group versus 0.60 U · kg^{-1} · day^{-1} ($P = 0.01$) and insulin dose at 6 months in DAISY of 0.36 U · kg^{-1} · day^{-1} versus 0.65 U · kg^{-1} · day^{-1} ($P = 0.005$). At 12 months, there was a trend for a lower dose in the DAISY children (0.55 vs. 0.73 U · kg^{-1} · day^{-1}) that did not reach statistical significance ($P = 0.09$) (Fig. 2*B*).

Children screened by DAISY for HLA genotypes at birth but not enrolled

Through collaboration with the SEARCH for Diabetes Study, which is attempting to document the incidence and prevalence of diabetes in several regions around the country including Colorado, 11 children who were initially screened as neonates

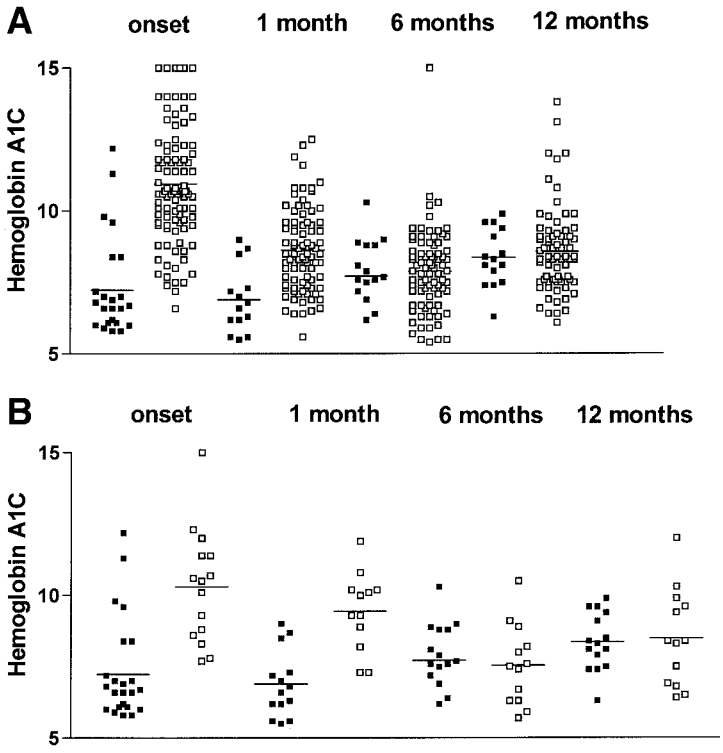

Figure 1—*HbA_{1c} in children diagnosed with diabetes in the DAISY (■) and community (□) groups at onset, 1, 6, and 12 months after diagnosis.* A: *HbA_{1c} in the entire group, significant differences are noted at onset and 1 month after diagnosis.* B: *HbA_{1c} in the group of individuals with a diabetic relative. Significant differences exist at onset and 1 month after diagnosis.*

by DAISY and not enrolled were identified. Seven were a moderate or high-risk genotype and refused enrollment. Three were a low-risk genotype and therefore not eligible for enrollment. One individual was at moderate risk at a time when DAISY was not enrolling moderate-risk individuals. Four of the eleven were hospitalized at onset of diabetes with DKA.

CONCLUSIONS — Prospective studies such as DAISY have taught us a great deal about the natural history of type 1 diabetes. These studies have identified children who are at a relatively high risk for diabetes and followed them over time to expression of islet cell autoimmunity and the development of clinical disease. Some individuals who express islet autoimmunity remain diabetes free for many years (24). In addition, there is no effective therapy for the prevention of disease in individuals identified as high risk by their HLA genotypes or the expression of islet autoimmunity. Therefore, the benefit of screening to the individuals screened has not yet been fully realized.

This report shows that children who participate in prospective follow-up were less often hospitalized and had milder metabolic abnormalities at diagnosis. Of note, during the follow-up time period of this current report, one 3-year-old girl died from cerebral edema and DKA. Her initial presentation was outside the metropolitan area of Denver, Colorado, and therefore was not included in this report. Given that type 1 diabetes is an autoimmune process that occurs over time (25), the observation that the children in the DAISY study were less metabolically abnormal at onset is likely the result of earlier monitoring and detection of mildly abnormal blood sugars.

There was a lack of difference in growth between the two groups of children. The number of children in each group may be too small to detect a difference. Therefore, we cannot come to any conclusions regarding this observation.

The major limitation of our study is the disparity between the numbers of children with a family history of type 1 diabetes in the community and DAISY groups, controlled for by performing comparisons between the community group as a whole and the DAISY group and also by performing similar comparisons in the group of community children with a family history of type 1 diabetes. The differences observed between community with a family history of type 1 diabetes and DAISY children were confirmed. Increased hospitalization in the community group with a family history of type 1 diabetes compared with the DAISY group was also observed ($P < 0.01$), indicating that individuals with a family history of disease are also at risk for severe disease at onset. This supports the argument that the major difference in the hospitalization rates, HbA_{1c}, and insulin dose between the community and DAISY children is not entirely due to the family history of diabetes in the DAISY group. The observed benefit in decreased hospitalization for DKA at onset in a high-risk population that is screened for β-cell autoimmunity and closely followed raises the question of whether there are benefits of screening for the risk factors of type 1 diabetes in the general population. The observed 36% hospitalization rate for those individuals screened as neonates but not followed suggests that screening as neonates may not be sufficient to provide protection, but larger studies are needed to confirm this observation.

The debate about screening for disease has a special meaning in the pediatric population (26). Children are not legally able to give informed consent, and the knowledge of a risk factor may have a long-lasting impact. If there is no effective treatment, the benefit of screening is questionable (26–28). In type 1 diabetes, known genetic risk factors are associated with an increased risk for disease, but the risk is by no means absolute. Therefore, there is still significant disagreement about screening for genetic markers of type 1 diabetes (HLA genotypes). Some argue that until there is an effective prevention strategy for type 1 diabetes, informing parents about high-risk HLA genotypes subjects them to undue stress and should not be done unless a prevention strategy is incorporated or is restricted to infants who are first-degree relatives of individuals with type 1 diabetes (29). Studies of parents of newborns participating in screening for diabetes have demonstrated that anxiety is largely related to protection of confidentiality

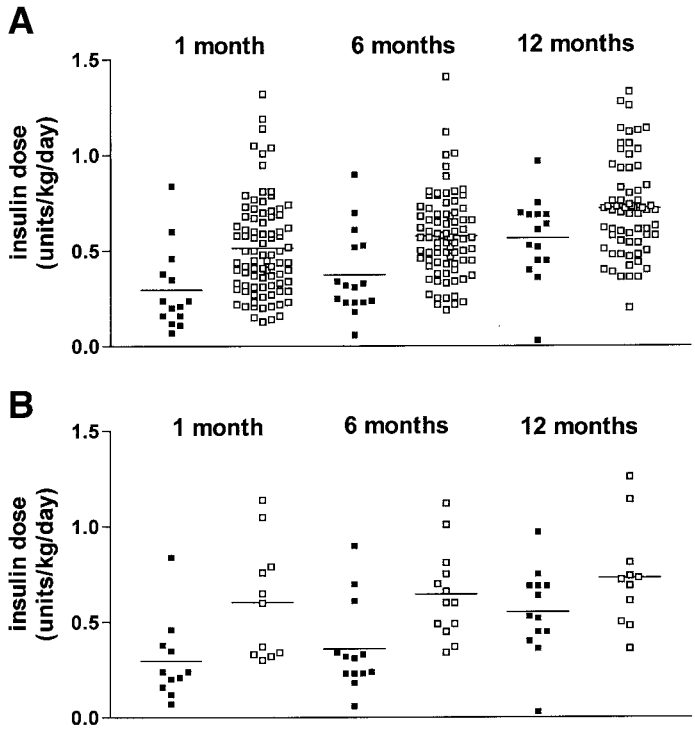

Figure 2—*Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$) in children diagnosed with diabetes in the DAISY (■) and community (□) groups at 1, 6, and 12 months after diagnosis.* A: *Insulin dose in the entire group. In the whole group, the insulin dose is significantly lower at all time points.* B: *Insulin dose in the group of individuals with a diabetic relative. In the group with a diabetic relative, statistical significance was reached at 1 and 6 months with a trend for a statistical difference at the 12-month time period.*

(30). Our group has shown that mothers of infants with high-risk HLA genotypes and mothers of infants with low-risk HLA genotypes have a similar reduction in maternal stress over time, which is independent of the neonate's HLA status (31). In the research setting, with appropriate control of biological specimens and support to participating families, the practice of HLA screening is accepted.

The second step in screening used by DAISY is the detection of islet cell autoantibodies. Some individuals persist with positive autoantibodies for years before the development of clinically evident diabetes and may never develop clinical disease, whereas others progress rapidly. The lack of diabetes in individuals who are autoantibody-positive may be either a function of time or may reflect autoimmunity that will never progress to diabetes. Knowledge of a positive islet autoantibody test likely has a psychological impact that varies over time and by individuals (32) and has been associated with behavioral change in an effort to prevent or delay the onset of disease (33).

The benefit of screening for islet autoimmunity in decreased hospitalization at onset must be balanced against the psychological impact of a positive test in individuals that may never develop the disease. Given the current evidence for psychological impact and behavioral change associated with screening for autoantibodies and the lack of effective prevention strategies, we do not currently recommend extending screening programs outside of the research setting. As improved prediction and effective prevention strategies are developed, screening the general population for disease becomes more feasible. Our study suggests that a formal cost-benefit analysis with data from more than one center following similar protocols would be useful. Given the severity of metabolic presentation, it is likely that in a large population some deaths and permanent morbidity are likely to be prevented. The "cost" of such prevention per quality of life years and confirmation of our single center experience is not yet available.

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