

Original Article

The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results

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Objectives: TrialNet's goal to test preventions for type 1 diabetes has created an opportunity to gain new insights into the natural history of pre-type 1 diabetes. The TrialNet Natural History Study (NHS) will assess the predictive value of existing and novel risk markers for type 1 diabetes and will find subjects for prevention trials.

Research design and methods: The NHS is a three-phase, prospective cohort study. In phase 1 (screening), pancreatic autoantibodies (glutamic acid decarboxylase, insulin, ICA-512, and islet cell antibodies) are measured. Phase 2 (baseline risk assessment) includes oral glucose tolerance tests (OGTTs) in antibody-positive subjects and estimation of 5-yr diabetes risks according to the OGTT and number of confirmed positive antibody tests. Phase 3 (follow-up risk assessments) requires OGTTs every 6 months. In phases 2 and 3, samples are collected for future tests of T-lymphocyte function, autoantibody isotypes, RNA gene expression, and proteomics. The primary outcome is diabetes onset.

Results: Of 12 636 relatives screened between March 2004 and December 2006, 605 (4.8%) were positive for at least one biochemical antibody. Of these, 322 were confirmed antibody positive and completed phase 2, of whom 296 subjects were given preliminary 5-yr diabetes risks of <25% ($n = 132$), $\geq 25\%$ ($n = 36$), and $\geq 50\%$ ($n = 128$) where the latter two categories represent different subjects based on number of confirmed positive antibodies (2, $\geq 25\%$; 3 or more, $\geq 50\%$) and/or an abnormal OGTT ($\geq 50\%$).

Conclusions: The NHS is identifying potential prevention trial subjects and is assembling a large cohort that will provide new natural history information about pre-type 1 diabetes. Follow-up to diabetes will help establish the biological significance and clinical value of novel type 1 diabetes risk markers.

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Recognition that type 1 diabetes is caused by immune-mediated loss of pancreatic β -cells has prompted a search for interventions that protect β -cells and improve long-term clinical outcomes (1, 2). The feasibility of studies testing this strategy has been proven in persons at risk for type 1 diabetes (prevention trials) (3–5) and in persons with type 1 diabetes and residual β -cell function (intervention trials) (6, 7). For these reasons, the National Institutes of Health, in cooperation with the American Diabetes Association (ADA) and Juvenile Diabetes Research Foundation, has formed Type 1 Diabetes – TrialNet to perform further prevention and intervention trials (8). In conducting prevention trials, TrialNet can also obtain new information about the natural history of pre-type 1 diabetes in relatives of persons with the disease. We describe in this study the aims, design, and initial results of the TrialNet Natural History Study of the Development of Type 1 Diabetes (NHS).

TrialNet is based on the Diabetes Prevention Trial-Type 1 (DPT-1), which screened more than 100 000 relatives for islet cell antibodies (ICA). ICA-positive subjects underwent diabetes risk assessments based on oral and intravenous glucose tolerance tests (IVGTTs) and were then entered into prevention trials (3, 5). In planning the NHS, TrialNet used data from a DPT-1 ancillary study (9), which showed that biochemical antibodies [glutamic acid decarboxylase antibodies (GADA), insulin autoantibodies (mIAA), and ICA-512 antibodies (ICA512A)/islet antigen-2 antibodies] can replace the more labor intensive and observer-dependent ICA assay as the first screening test.

We designed the NHS to address three main aims. First, we will validate the predictive accuracy of a new diabetes risk algorithm that uses biochemical antibodies rather than ICA as the first screening test. Second, we will collect samples for future assays of novel type 1 diabetes risk markers. The specimens (termed ‘mechanistic samples’) are being collected and stored according to procedures established in collaboration with the Immune Tolerance Network (10). Expected uses include frozen peripheral blood monocytes for T-lymphocyte functional assays, serum for antibody isotypes, RNA for gene expression studies, and plasma for proteomic studies. Third, the NHS will identify subjects for TrialNet prevention and intervention trials.

Methods

The protocol is available online (11). We based our definition of an NHS on standard sources (12–15) and are using a prospective cohort design divided into three phases: screening (phase 1), baseline risk assessment (phase 2), and follow-up risk assessments (phase 3). Sites in participating countries (USA, Canada, UK, Germany, Italy, Australia, and New Zealand) have local institutional review board approval and appropriate assurance with the Office for Human Research Protections. All test procedures and assays, including ICA (16) and biochemical antibodies (17) and the cut-points to define positive antibody tests, use established methods. In the 2005 Diabetes Antibody Standardization Program (DASP), the TrialNet biochemical antibody laboratory had respective sensitivities and specificities of 76 and 99% for GADA, 64 and 100% for ICA512A, and 58 and 99% for mIAA. In the 1998 Combinatorial Islet Antibody Workshop, the TrialNet ICA screening laboratory showed a sensitivity of 81% and specificity of 96%.

Figure 1 shows phase 1 antibody testing procedures. Inclusion criteria include age 1–45 yr and a relative with type 1 diabetes (first-degree relatives and second-degree or third-degree relatives for subjects less than 20 yr old). Type 1 diabetes in probands requires diabetes onset before age 40 yr and prescription of insulin within a year of diagnosis. The requirement for insulin therapy within 1 yr in the proband reflects a compromise between a shorter interval (e.g., 3–6 months) that will be more specific for type 1 diabetes, but that is also more restrictive because it will disqualify some probands who have type 1 diabetes, and a longer interval that increases the chance for enrolling subjects with probands who clearly have type 2 diabetes. It is also consistent with the time to start of insulin therapy in probands previously used in the DPT-1 prevention trials (3, 5).

Subjects with at least two positive tests for any one of the four antibodies in the phase 1 samples are eligible for phase 2 (Fig. 1). Subjects who are discordant for a specific antibody on the first two samples (e.g., GADA positive on the first test but GADA negative on the second test) are asked to provide a third sample to resolve their baseline antibody status. Thus, if two out of three tests are positive for GADA, the subject is

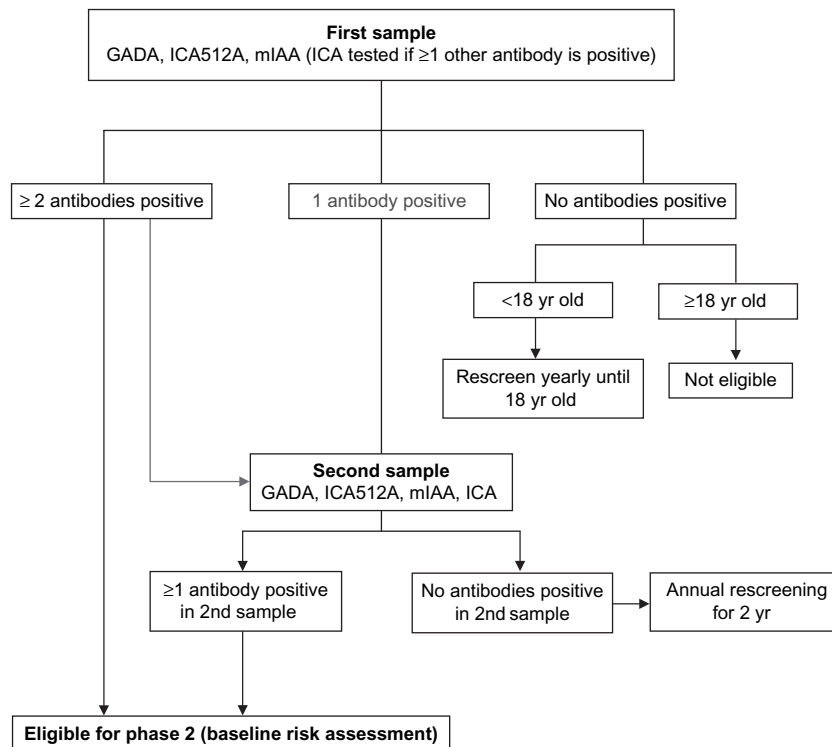


Fig. 1. Phase 1 antibody screening procedure. Subjects with at least two positive antibodies on the first sample can proceed directly to phase 2 or can provide a second sample in phase 1 before entering phase 2. ICA positivity is defined by values ≥ 10 Juvenile Diabetes Foundation units (16). Definitions for GADA, ICA512A, and mIAA positivity are based on values exceeding the 99% in normal controls (17). GADA, glutamic acid decarboxylase antibodies; ICA, islet cell antibodies; ICA512A, antibodies to ICA-512; mIAA, insulin autoantibodies.

defined as 'confirmed GADA positive'. Other phase 2 tests include an oral glucose tolerance test (OGTT), hemoglobin A_{1c} (A1C) level, and human leukocyte antigen (HLA) typing. Subjects with protective type 1 diabetes genotypes are not excluded. The OGTT includes samples for glucose levels at 0, 30, 60, 90, and 120 min. Insulin and C-peptide levels are also being measured at these times for, respectively, estimates of insulin sensitivity by the homeostatic model assessment – insulin resistance and endogenous insulin secretion.

At completion of phase 2, glucose levels during the OGTT and the number of confirmed positive antibodies are being used to assign subjects to preliminary 5-yr diabetes risk categories of ≥ 50 , ≥ 25 , or $< 25\%$ (Fig. 3) (see also *Protocol modifications* below). We are not masking subjects or investigators with respect to projected diabetes risks.

Subjects completing phase 2 are eligible for phase 3 and are asked to return every 6 months for an OGTT, A1C level, and antibody tests. We are also enrolling former DPT-1 subjects who have not developed diabetes into phase 3 to extend observations on the long-term risk for diabetes in that cohort. At all phases, residual blood samples including DNA are being stored at a TrialNet or NIH repository laboratory. The mechanistic samples are being collected in phases 2 and 3.

Protocol modifications

Two protocol changes (effective from February 2007) have been made since the NHS was implemented in February 2004. First, the antibody criteria determining phase 2 eligibility were modified. Whereas the previous definition required that at least one specific antibody be positive on two separate tests, the new definition (see above) was made to match antibody criteria that are determining subject eligibility for the TrialNet randomized trial of oral insulin to prevent type 1 diabetes that is now underway (www.diabetestrialnet.org, accessed 12 November 2007). We also projected that the risk for diabetes in persons with at least two positive tests for any antibodies warranted closer follow-up in phase 3. In the *Results* below, the original antibody criteria defining eligibility for phase 2 are reported.

Second, the original risk algorithm assigned subjects to 5-yr diabetes estimates of < 25 , 25–50, or $> 50\%$ based on results of the OGTT, number of confirmed positive antibodies, and, in selected cases, an impaired first-phase insulin response (FPIR) during the IVGTT. The FPIR was used in subjects with a normal OGTT and exactly two confirmed positive antibodies to discriminate between 5-yr diabetes risks of 25–50 or $> 50\%$. However, we found that few ($\sim 10\%$) subjects needed the FPIR for risk stratification and that the

projected power to assess the added predictive value of the FPIR over other risk markers would remain low even upon screening thousands of subjects. Other DPT-1 analyses also suggested that the FPIR added little additional predictive accuracy over glucose and C-peptide levels obtained during the OGTT in antibody-positive relatives (18). Given this, and the burden to subjects in performing the IVGTT, we omitted the test from the NHS. As a result, using the FPIR to refine risk beyond a base estimate of $\geq 25\%$ in subjects with exactly two confirmed positive antibodies was no longer possible. We therefore altered the 5-yr risk categories to $\geq 50\%$, $\geq 25\%$, or $< 25\%$ where the risk categories of $\geq 50\%$ and $\geq 25\%$ identify different subjects based on the number of confirmed positive antibodies (three or more antibodies for subjects in the $\geq 50\%$ group and two antibodies for subjects in the $\geq 25\%$ group) (Fig. 3). In the *Results* below, we have reclassified subjects according to the modified risk algorithm.

Statistical analysis and sample size estimation

The primary outcome is diabetes mellitus by ADA criteria (19). The prevalence of each risk category will be described as a function of subject characteristics. Cumulative diabetes incidences and hazard rates will be assessed within risk categories. Covariate effects on diabetes risks (e.g., age, gender, and the time to starting insulin in the proband) will be analyzed by proportional hazards regression models (20). Formal analyses will be conducted after 250 subjects in the $\geq 50\%$ risk category have developed diabetes. This will provide a 95% confidence band of (55 and 64%) for a cumulative incidence of 60% and will also provide 85% power to detect a 30% difference in the hazard rate between two equal-sized groups for a binary covariate. We will not necessarily exclude prevention trial subjects from natural history analyses, in part because subjects allocated to untreated control arms in prevention trials may still contribute unbiased natural history information. To test this assumption, we will compare diabetes risk between subjects who are eligible and randomized to control groups with the risk in subjects who are eligible but who do not enter a prevention trial.

Results

We report in this study the results for 12 636 TrialNet subjects who entered phase 1 between March 2004 and January 2006 and for 322 subjects who entered phase 2 by 31 December 2006 (Fig. 2). By December 2006, 219 TrialNet subjects and 54 former DPT-1 subjects had entered phase 3, of whom 7 and 2 subjects, respectively, developed diabetes. The time for follow-up, and therefore number of new diabetes cases, is insufficient to draw meaningful conclusions about risk prediction. Diabetes outcomes will be reported in future publications.

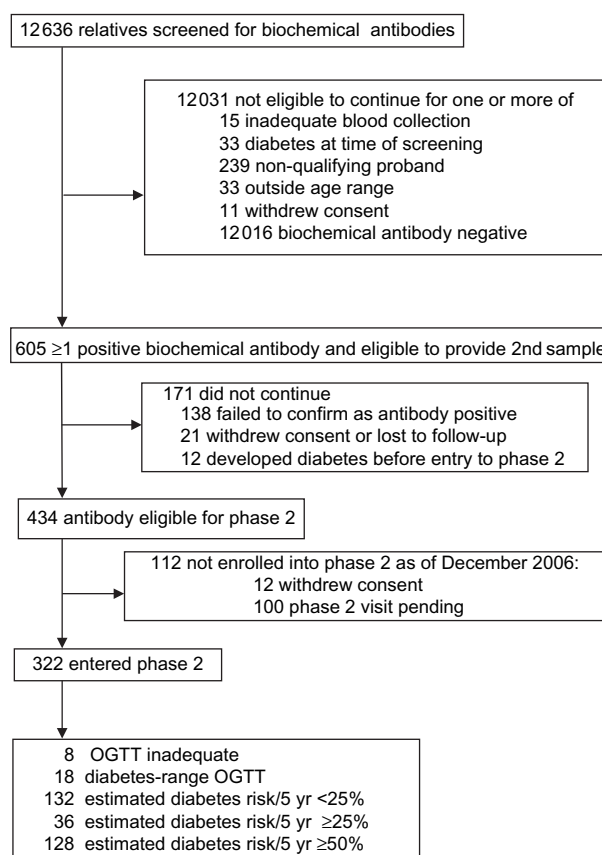


Fig. 2. Enrollment of subjects from March 2004 to December 2006. Criteria for antibody eligibility for phase 2 are based on the definition used before February 2007 (see Methods). 'Lost to follow-up' refers to subjects who failed to return for further testing despite repeated attempts to contact them or their caregiver. OGTT, oral glucose tolerance test.

Table 1 shows baseline characteristics of phase 1 and 2 subjects. More than 90% had at least one first-degree relative with T1D, and 55% were less than 21 yr old. Most subjects (95%) were ineligible for phase 2 because they were negative for the biochemical antibodies on the first phase 1 sample (Fig. 2). Among 605 subjects with at least one positive biochemical antibody, 72% met eligibility criteria for phase 2, of whom 74% entered phase 2 (Fig. 2).

Table 2 shows NHS antibody test results in the first phase 1 sample and antibody results in a subset of more than 17 000 subjects screened in DPT-1 (9). Approximately 5% (605/12 636) of NHS subjects had at least one positive biochemical antibody on their first sample. As in the DPT-1, GADA was the most frequent positive antibody (3.6%) on the first test. Most (57%) antibody-positive subjects had a single positive antibody; this group comprised 2.8% of all screened subjects.

Confirmation rates for specific antibodies on subsequent testing in the NHS ranged between 74% (ICA) and 88% (GADA) (Table 2). As expected, a strong association was seen between the number of positive antibodies on the first test and confirmation of

Table 1. Phase 1 and phase 2 subjects' characteristics

	Phase 1 (n = 12 636)	Phase 2 (n = 322)
Mean age (SD) (yr)	21.8 (14.8)	19.4 (14.3)
Age range (yr) (%)		
1-5	14	15
6-10	19	26
11-15	15	16
16-20	7	6
21-25	2	2
26-45	43	35
Female (%)	59	58
Race (%)		
White	88	90
African-American	3	2
Asian	1	2
Others	9	6
Ethnicity (%)		
Hispanic/Latino	13	9
Others	87	91
Family history of type 1 diabetes* (%)		
First-degree relative	91	94
Second-degree relative	17	18
Third-degree relative	9	8
One affected relative	77	73
Two or more affected relatives	20	27
HLA DQB1*0602 (%)	Not done	5

*Subjects could have two or more relatives, of different degrees, with type 1 diabetes.

antibody positivity on repeat testing. Thus, 98% of subjects with at least two positive antibodies on the first test were positive for at least one antibody on subsequent testing, whereas 74% of subjects with only one positive antibody on the first test were confirmed positive on subsequent testing (Table 2). In subjects with a single positive biochemical antibody test on the first sample, failure to confirm antibody positivity for the specific biochemical antibody on subsequent testing was associated with lower antibody levels on the first test. Thus, the median GADA value among 44 subjects positive on the first test but who did not confirm GADA positive on a subsequent test was 0.061 vs. a median GADA value of 0.300 in 318 subjects who subsequently confirmed positive for GADA ($p < 0.0001$, Wilcoxon two-sample test). Corresponding values for ICA512A were 0.067 in 21 subjects who did not confirm positive for ICA512A vs. 0.672 in 124 subjects who did ($p < 0.0001$); for mIAA, the values were 0.018 in 40 subjects not confirming positive vs. 0.041 in 117 subjects who did ($p = 0.0002$).

Of the 322 subjects enrolled in phase 2, 314 completed the OGTT and 8 subjects' OGTT were inadequate (e.g., samples hemolyzed, missing samples at 0 or 120 min). In the 314 subjects with an adequate OGTT, the projected 5-yr diabetes risks were $<25\%$ ($n = 132$), $\geq 25\%$ ($n = 36$), and $\geq 50\%$ ($n = 128$) based on the modified risk algorithm (Fig. 3). Eighteen subjects had an abnormal OGTT consistent with diabetes. The

Table 2. Antibody test results

	NHS (n = 12 636)	DPT-1* (9) (n = 17 207)
Number of subjects with a positive Ab test on first sample, n (%)		
One Ab	347 (2.8)	1009 (5.9)
Two Abs	125 (1.0)	193 (1.1)
Three Abs	91 (0.7)	147 (0.8)
Four Abs	42 (0.3)	54 (0.3)
Number of subjects positive by specific Abs on first sample, n (%)		
GADA	452 (3.6)	688 (4.0)
ICA512A	205 (1.6)	276 (1.6)
mIAA	203 (1.6)	437 (2.5)
ICA*	178	651 (3.8)
Number of subjects positive for one or more biochemical Ab on first sample, n (%)	605 (4.8)	1076 (6.2)
Confirmation rates by Ab type†, n (%)		
GADA	318/362 (88)	
ICA512A	124/145 (86)	
mIAA	117/157 (75)	
ICA	102/139 (74)	
Confirmation rates by number of positive Abs on first sample†, n (%)		
One Ab positive	211/284 (74)	
Two Abs positive	91/94 (97)	
Three Abs positive	67/67 (100)	
Four Abs positive	33/33 (100)	
Two or more Abs positive	191/194 (98)	

Ab, antibody; DPT-1, Diabetes Prevention Trial-Type 1; GADA, glutamic acid decarboxylase antibodies; ICA, islet cell antibodies; ICA512A, antibodies to ICA-512; mIAA, insulin autoantibodies.

*ICA is only tested in TrialNet subjects with at least one positive biochemical antibody but was tested in all DPT-1 subjects irrespective of biochemical antibody results.

†Based on up to three samples being tested for antibodies in phase 1 and phase 2 more than 1 yr, where a confirmed positive antibody required that a specific antibody be positive on at least two samples. Subjects could be confirmed positive for more than one antibody.

OGTT results in the remaining subjects were normal ($n = 217$) or showed impaired glucose tolerance (IGT) ($n = 46$), impaired fasting glucose (IFG) ($n = 22$), or IGT and IFG ($n = 11$). Subjects with an abnormal OGTT including diabetes had a higher body mass index (BMI) compared with subjects with normal OGTTs (respective mean BMIs: 23.9 vs. 21.8 kg/m², $p = 0.023$, Student's *t*-test).

Discussion

Natural history studies in antibody-positive relatives of persons with type 1 diabetes are neither new nor rare, beginning with the Bart's-Windsor study in 1978 that showed ICA predicted diabetes (21). Since then, more than 250 natural history studies have been reported based on a literature scan for a systematic review of natural history studies that we are currently undertaking. These studies have defined and validated markers

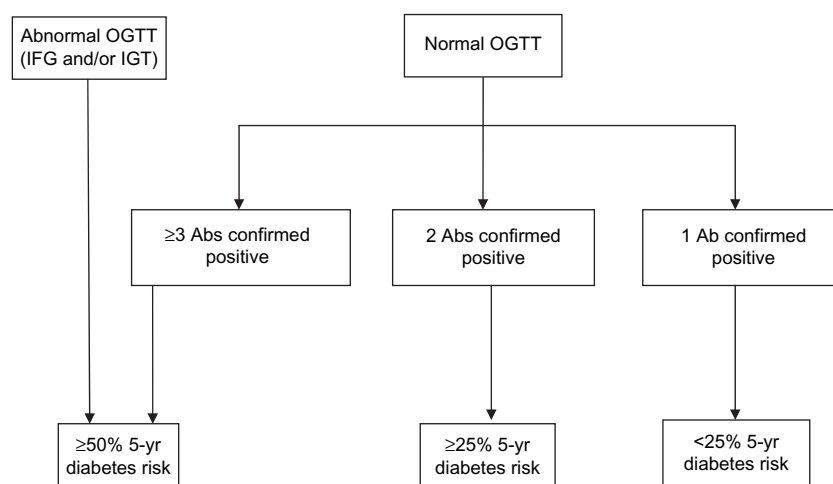


Fig. 3. Five-year diabetes risk estimates. Confirmed antibody positivity requires that the specific antibody (GADA, ICA512A, mIAA, or ICA) be positive on at least two separate tests in phase 1. The risk categories of ≥ 25 and $\geq 50\%$ apply to mutually exclusive subject groups according to the number of confirmed positive antibodies and presence or absence of an abnormal glucose tolerance test. GADA, glutamic acid decarboxylase antibodies; ICA, islet cell antibodies; ICA512A, antibodies to ICA-512; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; mIAA, insulin autoantibodies; OGTT, oral glucose tolerance test.

of future type 1 diabetes to the point where definitive prevention trials have become possible (3–5).

Despite this, important natural history questions remain unanswered. For example, the capacity of T-lymphocyte functional assays to predict future type 1 diabetes, and thus the exact role T-lymphocytes play in human β -cell loss, is unclear beyond general agreement that they are centrally important (22). Similarly, the impact of insulin sensitivity on progression to type 1 diabetes is uncertain (23–26). Answers to these and other questions will help TrialNet develop type 1 diabetes preventions in two ways. First, better understanding of the natural history of pre-type 1 diabetes can direct decisions about treatments worth testing. For example, testing interventions that improve insulin sensitivity, of which there are now several in routine use in clinical practice in patients with type 2 diabetes, will become attractive if insulin resistance is confirmed to increase the risk for future type 1 diabetes over other readily available risk markers. Second, the efficiency of clinical trials can be improved through more accurate diabetes prediction in subjects allocated to control groups within trials. Additional justification for the NHS arises from earlier detection of type 1 diabetes through antibody screening and, with that, reduction in risk for diabetic ketoacidosis at first presentation (27).

The feasibility of prevention trials depends heavily upon antibody screening rates and the frequency of antibody-positive relatives. For example, for each subject randomized in the DPT-1 trials, some 145 persons were tested for ICA (3, 5). The NHS's practical aim of finding subjects for prevention trials therefore makes the rates of antibody screening and antibody positivity important determinants of TrialNet's success. Till December 2006, the NHS screened 23 951 relatives for antibodies over 30 months (750 subjects/month). As

a benchmark, the DPT-1 screened 990 subjects/month over 8 1/3 yr (5). However, expansion of TrialNet to countries outside USA and the availability in 2007 of the oral insulin prevention trial as an option for some antibody-positive NHS subjects have led to an increase in screening such that the 2007 rate (1340/month) exceeds that of the DPT-1.

Comparison of antibody positivity rates on the first screening test between the DPT-1 and the NHS must consider the major difference in screening procedures: the DPT-1 screened with ICA (9), whereas the NHS screens with biochemical antibodies. The difference between the two studies in rates of single antibody-positive subjects on the first test is one example of this, where at least some of the difference in rates (NHS = 2.8% vs. DPT-1 = 5.9%) can be accounted for by exclusively ICA-positive subjects. This group, which cannot be ascertained by the NHS screening procedure, occurred in 1.9% ($n = 327$) of screened DPT-1 subjects (9). However, there is more congruence in rates of antibody positivity on the first screening test between the two studies in respect to specific biochemical antibodies and the number of subjects who are positive for two or more antibodies (Table 2). The failure to confirm antibody-positive tests in some 25% of single biochemical antibody subjects in the NHS was clearly associated with marginally positive test results on the first sample. Raising the cut-point to define antibody positivity would reduce the number of false positives but comes at the cost of missing individuals who would confirm positive on two tests. This finding affirms the value of repeating antibody testing before judging individuals' risks or enrolling them in a prevention trial.

The decision to screen persons more than age 25 yr in the NHS follows from TrialNet's plan to enter antibody-positive older relatives into prevention trials.

This decision was made despite the fact that screening older relatives is less cost-effective than screening younger relatives, where cost-effectiveness refers in this context to the costs incurred to identify and enroll enough subjects to detect a treatment effect of interest. The cost-effectiveness of a trial that includes older subjects will not be as good because the rates of positive antibodies, including multiple antibodies, and risk for future diabetes are lower in older compared with younger subjects. For example, in the European Nicotinamide Diabetes Intervention Trial (ENDIT), more than 80% of subjects progressing to diabetes within 5 yr were less than 25 yr old at screening (28). Thus, at least three times as many older subjects relative to younger subjects needed to be screened to find one person who progressed to diabetes.

However, the cost-effectiveness of a trial in those terms does not address the larger question of cost-effectiveness of screening and preventing type 1 diabetes in older persons. For example, a safe and effective prevention for type 1 diabetes in subjects between age 25 and 45 yr could yield sufficient cost savings that justify, if not completely outweigh, the added costs needed to identify and treat at-risk older persons. Higher costs to screen older subjects could also be offset by a prevention that is more effective in older subjects. This is plausible because the autoimmune process appears to be less aggressive in older persons. Although modeling studies can estimate the cost-effectiveness of different screening strategies according to age, they depend on important assumptions about treatment effects. Such assumptions are best confirmed, or refuted, in randomized trials that test preventive treatments in subjects across a wide age range.

An important methodological issue in the NHS extends from our plan to include data from subjects who enter prevention trials in natural history analyses. The advantage in combining data across prevention trials and the NHS cohort is greater power to detect relationships between risk markers and subsequent diabetes, including more power to detect independent relationships between diabetes and multiple risk markers that may be confounded. This validity of this approach depends on whether there are differences in the natural history of subjects who enter a prevention trial compared with those who do not, where an important clinical measure of the natural history is diabetes outcome. A recent Cochrane Systematic Review has addressed this question more generally, namely, 'Do outcomes in subjects who participate in randomized controlled trials differ compared with similar subjects who do not participate?'. There were no differences in outcomes between the two types of subjects across a variety of different problems and diseases (29).

However, if real differences in diabetes risk exist between subjects who enter prevention trials vs. those who do not, then natural history analyses based on

combined data will yield biased risk estimates. Such differences can be ascribed to 'trial effects' and include placebo responses, unmeasured baseline differences in subjects who choose not to enter a prevention trial despite fulfilling all other entry criteria, and differences in procedures to ascertain diabetes between the NHS and the prevention trials. We have minimized the latter by matching our approach to diabetes ascertainment in the NHS to the approach that is being used in current and future prevention trials including the oral insulin prevention trial. We cannot rule out placebo effects or unmeasured differences in baseline characteristics beyond testing for and excluding heterogeneity in diabetes risks between subjects who are eligible for but who do not enter a prevention trial vs. eligible subjects randomized to a trial's control group. We also do not exclude a similar analytic strategy, as has been used in recent natural history publications from the DPT-1 and ENDIT Study Groups (28, 30), that include data from subjects randomized to active treatment arms in prevention trials but in which it is found that the test therapies do not affect diabetes risk.

Other large natural history studies, and prevention trials that will yield important natural history information, are now underway including The Environmental Determinants of Diabetes in the Young (TEDDY) (31), The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) (32), and the Finnish IDDM Prediction and Prevention Project (DIPP) (33). It is useful to place the TrialNet NHS in the context of those other studies. Each has a focus on genetically high-risk subjects starting with a positive family history of type 1 diabetes, although TEDDY and DIPP are also enrolling subjects without a family history but with high-risk HLA genotypes. Important differences include ascertainment of the cohorts at birth in TEDDY, TRIGR, and DIPP vs. enrolling subjects after age 1 yr in the NHS; the use of antibodies as a baseline determinant of eligibility in the NHS vs. development of antibodies as important secondary outcomes in TEDDY, TRIGR, and DIPP; and a focus in TEDDY, DIPP, and TRIGR not shared by the NHS on environmental factors that may cause β -cell autoimmunity. These studies have much in common including overlap among investigators across the study groups. In aggregate, these and other studies will generate large, prospectively followed cohorts that will comprehensively assess the natural history of pre-type 1 diabetes in high-risk persons from birth to middle age.

In conclusion, the TrialNet NHS is identifying subjects for participation in type 1 diabetes prevention trials and is assembling a large cohort of at-risk persons that will yield new natural history information about pre-type 1 diabetes. Follow-up to diabetes onset is underway and will establish the biological significance and clinical value of both established and novel type 1 diabetes risk markers.

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