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Clinical Research Article

Barriers to Screening: An Analysis of Factors Impacting Screening for Type 1 Diabetes Prevention Trials

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Abstract

Context: Participants with stage 1 or 2 type 1 diabetes (T1D) qualify for prevention trials, but factors involved in screening for such trials are largely unknown.

Objective: To identify factors associated with screening for T1D prevention trials.

Methods: This study included TrialNet Pathway to Prevention participants who were eligible for a prevention trial: oral insulin (TN-07, TN-20), teplizumab (TN-10), abatacept (TN-18), and oral hydroxychloroquine (TN-22). Univariate and multivariate logistic regression models were used to examine participant, site, and study factors at the time of prevention trial accrual.

Results: Screening rates for trials were: 50% for TN-07 (584 screened/1172 eligible), 9% for TN-10 (106/1249), 24% for TN-18 (313/1285), 17% for TN-20 (113/667), and 28% for TN-22 (371/1336). Younger age and male sex were associated with higher screening rates for prevention trials overall and for oral therapies. Participants with an offspring with T1D showed lower rates of screening for all trials and oral drug trials compared with participants with other first-degree relatives as probands. Site factors, including larger monitoring volume and US site vs international site, were associated with higher prevention trial screening rates.

Conclusions: Clear differences exist between participants who screen for prevention trials and those who do not screen and between the research sites involved in prevention trial screening. Participant age, sex, and relationship to proband are significantly associated with prevention trial screening in addition to key site factors. Identifying these factors can facilitate strategic recruitment planning to support rapid and successful enrollment into prevention trials.

Key Words: type 1 diabetes, prevention, enrollment, recruitment, drug clinical trials

Abbreviations: Ab, antibody; HbA1c, hemoglobin A1c; IRB, institutional review board; NHW, non-White Hispanic; OR, odds ratio; OGTT, oral glucose tolerance test; PTP, TrialNet Pathway to Prevention study.

The global incidence of type 1 diabetes is about 15 per 100 000 persons, with incidence increasing by 2% to 5% annually and prevalence trending upwards [1–3]. With prevalence in youth of 1.93 per 1000 in the United States, type 1 diabetes represents 1 of the most common chronic childhood diseases and generates profound medical costs [2, 4, 5]. The rise in disease incidence and prevalence brings concerns of future insulin availability, especially in underdeveloped and developing countries [1–3]. As such, there is a great need for research investigating the natural history of disease and potential therapies for treatment and prevention. Clinical research has reframed the disease as one that progresses sequentially through distinct stages and natural history studies have identified genetic predisposition, age at islet autoimmunity, and type of first islet autoantibody (Ab) as significant risk factors for development of type 1 diabetes [1–3, 6, 7].

Evidence of disease can first be seen in stage 1, in which β-cell autoimmunity is characterized by presence of 2 or

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more islet Abs and normal glucose tolerance [6]. Stage 2 occurs when a person with multiple Abs begins to have metabolic abnormalities (dysglycemia) but remains clinically asymptomatic [6]. Stage 3 is considered the start of symptomatic disease, when a patient is diagnosed with clinical diabetes and insulin replacement therapy is usually initiated [6, 8]. Identification of disease in the presymptomatic stages can reduce the rate of diabetic ketoacidosis at diagnosis and facilitate better long-term glycemic control [9–11]. Subsequently, early diagnosis of disease significantly improves long-term health outcomes, including better diabetes control (measured through hemoglobin A1c [HbA1c]), which is associated with decreased diabetes-related complications [11, 12].

Type 1 Diabetes TrialNet (TrialNet) is an international network whose mission is to prevent type 1 diabetes and stop disease progression. The TrialNet Pathway to Prevention study (PTP; ClinicalTrials.gov reg. no. NCT00097292) offers serial Ab testing for the development of islet autoimmunity and monitors disease progression with an oral glucose tolerance test (OGTT) and HbA1c [13–16]. Participants found to be in the presymptomatic stages of disease, and therefore at a higher risk of developing type 1 diabetes, are monitored for disease progression through the PTP study and offered clinical trial opportunities to prevent or delay the onset of type 1 diabetes.

Through TrialNet, the first positive clinical trial has been shown to delay the onset of type 1 diabetes. In this pivotal trial investigating anti-CD3 monoclonal antibody (teplizumab) treatment in the stage 2 population (TN-10 trial), the onset of disease was delayed by almost 3 years in those receiving active treatment [17, 18]. Teplizumab was recently approved by the US Food and Drug Administration as the first drug to delay the onset of type 1 diabetes, and most of the supporting data came from this TN-10 trial. However, enrollment for the TN-10 trial spanned more than 6 years and less than 10% of those eligible screened for trial inclusion. Despite evidence supporting the benefits of delaying or preventing type 1 diabetes, studies investigating preventive therapies such as teplizumab face similar barriers to other clinical trials, with a small percent of eligible participants enrolling into trials [11, 12, 19]. By understanding the factors impeding prevention trial screening and enrollment, improvements can be made in study design, recruitment strategy, and research site support, which ultimately may expedite prevention trial advancement. The aim of the current study was to identify and define the potential factors influencing screening into 5 recent TrialNet prevention trials by analyzing participant and site-specific characteristics.

Materials and Methods

Study Population

This study included TrialNet PTP monitoring participants who were eligible for a TrialNet prevention trial. The PTP study identifies individuals at a greater risk of developing type 1 diabetes and provides monitoring for disease progression [13]. The start of the autoimmune process is assessed in the study's screening phase through testing of Abs, including islet cell Abs, and Abs to glutamic acid decarboxylase, islet antigen 2, insulin, and zinc transporter 8 [6, 13, 20, 21]. In the monitoring phase, participants who are positive for 2 or more islet Abs undergo metabolic assessments to determine glycemic status and disease staging [6, 13]. As determined by OGTT and HbA1c, stage 1 participants with normal metabolic function (normoglycemic) are seen annually for metabolic assessment; dysglycemic stage 2 participants are seen semiannually [6, 13]. In addition to being monitored for disease progression, stage 1 and stage 2 participants are considered for accruing TrialNet prevention trials based on previous and current PTP results.

This study included PTP monitoring participants who were eligible for at least 1 of the following prevention trials: Oral Insulin for Prevention of Diabetes in Relatives At Risk for Type 1 Diabetes Mellitus (TN-07 trial, ClinicalTrials.gov reg. no. NCT00419562), Anti-CD3 MAB (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus (TN-10 trial, ClinicalTrials.gov reg. no. NCT01030861), CTLA-4 Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus (TN-18 trial, ClinicalTrials.gov reg. no. NCT01773707), Exploring Immune Effects of Oral Insulin in Relatives at Risk for Type 1 Diabetes Mellitus (TN-20 trial, ClinicalTrials.gov reg. no. NCT02580877), and Hydroxychloroquine for Prevention of Abnormal Glucose Tolerance and Diabetes in Individuals At-Risk for Type 1 Diabetes Mellitus (TN-22 trial, ClinicalTrials.gov reg. no. NCT03428945) [17, 18, 22, 23].

Prevention trial eligibility was defined based on retrospective PTP data review, considering participant Ab and OGTT status at the time of prevention trial accrual (Fig. 1). Based on Abs, OGTT, and HbA1c status obtained from PTP monitoring visits completed during prevention trial accrual, stage 1 participants were eligible for TN-07 Oral Insulin (enrollment, March 2007-December 2015), TN-18 Abatacept (enrollment, March 2013-August 2019), TN-20 Oral Insulin (enrollment, January 2016-January 2017), and TN-22 Hydroxychloroquine (enrollment, ongoing as of May 31, 2021; dataset, beginning September 2018); stage 2 participants were eligible for TN-10 Teplizumab (enrollment, July 2011-September 2017), and a small subset of stage 2 participants were also eligible for TN-20 [17, 18, 22, 23]. Prevention trial characteristics are further described in Table 1.

The PTP study and the prevention trials were approved by an institutional review board (IRB) or ethics committee and were monitored by an external data safety monitoring board. Before study entry, informed consent was obtained from all participants. Consent of the parent or legal guardian was obtained for participants aged <18 years. Depending on the study and local regulatory requirements, assent was obtained for children aged >6 to 8 years.

Statistical Analyses

Differences in demographic and clinical characteristics as well as site-specific factors were compared between trial-eligible participants who screened for a prevention trial vs those who did not. Univariate and multivariate logistic regression models were used to identify significant factors.

Participant variables evaluated included age at initial PTP Ab screening, age at multiple Ab positivity (ie, stage 1 type 1 diabetes classification), age at eligibility for trial, sex, self-reported race, self-reported ethnicity, and relationship to proband affected with type 1 diabetes (parent, sibling, offspring). Age was assessed as categorical and continuous variables. For the analyses of age as a categorial variable, participants were categorized as children (aged <12 years) or adolescents and adults

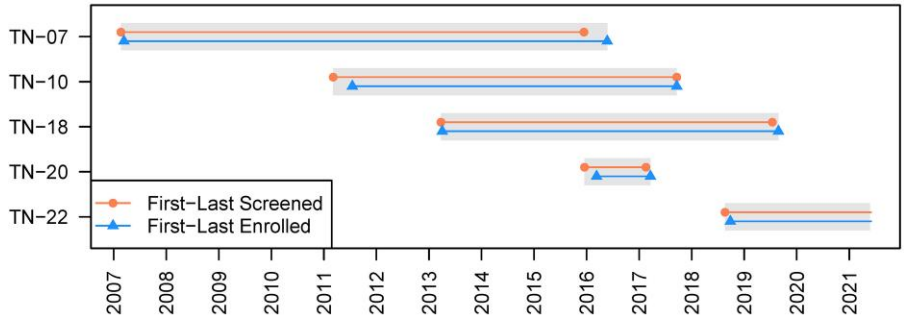

Figure 1. Enrollment timelines for TrialNet prevention trials included in the analysis. Prevention trial enrollment timelines based on screening milestones (first and last participant screened for each prevention trial) and enrollment milestones (first and last participant enrolled into each prevention trial).

(aged ≥12 years). Because of the small sample size of some groups, race and ethnicity were combined for logistic regression analyses. Research site variables included location (US vs international) and site volume. Site volume was analyzed by number of PTP participants monitored annually at the site. To account for overlap in eligible participants across the studies over time, participant data were weighted by the number of studies for which they were eligible when analyzing combined trials.

Factors with P values < 0.1 in univariate analyses were included in multivariate analyses. Because the different age variables are closely correlated, age at multiple Ab positivity only was included as a categorical variable in the multivariate analyses. P values < 0.05 were considered statistically significant.

Results

Characteristics for eligible and screened participants for each trial are shown in Table 2.

In this analysis (dataset as of May 31, 2021), the only accruing TrialNet prevention trial is the TN-22 study. Of participants eligible for each prevention trial, screening rates were as follows: 49.8% for TN-07 (584 screened/1172 eligible), 8.5% for TN-10 (106/1249), 24.4% for TN-18 (313/1285), 16.9% for TN-20 (113/667), and 27.8% for TN-22 (371/1336). Because route of investigational product administration was determined to be a key study characteristic affecting participant enrollment, analyses were conducted looking at the trials by investigational product administration route (Figs. 2 and 3) as well as each trial individually (Figs. 4 and 5). Univariate and multivariate results are presented as odds ratios (OR) and 95% CIs. Univariate analyses looking at potential factors associated with prevention screening in trial-eligible participants are shown in Figs. 2 and 4 and multivariate analyses are shown in Figs. 3 and 5.

Participant Factors

When all trials were grouped, younger age was associated with an increased likelihood of screening in univariate analysis. Younger age also was associated with an increased likelihood of screening for the oral drug trials (TN-07, TN-20, and TN-22) when evaluated together and individually. Younger age at initial PTP screening, younger age at the time of initial multiple Ab positivity (age at stage 1), and younger age at the time of trial eligibility were all associated with increased likelihood of trial screening for oral drug trials (all $P < 0.001$). These results were also significant when TN-07 and TN-22 were analyzed individually. In TN-20, only younger age at stage 1 and younger age at the time of trial eligibility were significant. Older age was associated with an increased likelihood of screening for the IV infusion trials (TN-10 and TN-18) and the TN-18 trial individually. Older age at initial PTP screening, older age at stage 1, and older age at the time of trial eligibility were associated with an increased likelihood of screening for IV infusion trials (all $P < 0.05$); these results were also significant when TN-18 was analyzed individually (all $P < 0.05$).

When all trials were grouped, younger age was again associated with an increased likelihood of screening in multivariate analyses. Age <12 years at stage 1 stayed significantly associated with screening in the oral drug trials and in TN-07 and TN-22 individually (all $P < 0.05$). Inversely, age ≥12 years was associated with screening for the intravenous infusion trials and for TN-18 individually (all $P < 0.01$).

In univariate and multivariate analyses, race and ethnicity were not found to be significant when the trials were analyzed together, likely because the TrialNet participant population mainly consists of non-Hispanic White (NHW) participants (86% to 90%). However, significance was found when the trials were analyzed separately. Race and ethnicity were found to be significant participant factors in trial screening for TN-07 and TN-10. In the TN-07 trial, non-Hispanic non-White participants were less likely to screen compared with NHW participants (univariate: OR, 0.60; 95% CI, 0.36-1.00; multivariate: OR, 0.88; 95% CI, 0.77-0.99). For TN-10, Hispanic participants were less likely to screen for trial inclusion than NHW participants (univariate: OR, 0.24; 95% CI, 0.08-0.78; multivariate: OR, 0.92; 95% CI, 0.87-0.97). Significance was not found for any other race or ethnicity analyses across the prevention trials.

Family history of type 1 diabetes played a significant role in the univariate analyses when the trials were grouped as a whole and when the trials were grouped by investigational product administration route. Participants with an offspring with type 1 diabetes showed lower rates of screening for all trials and oral drug trials compared with participants with other first-degree relatives as probands (OR, 0.56; 95% CI, 0.43-0.74, and OR, 0.42; 95% CI, 0.29-0.61, respectively). Family history stayed significant in the multivariate analyses of all trials and oral drug trials, but the association was not as strong (OR, 0.94; 95% CI, 0.91-0.98, and OR, 0.93; 95% CI, 0.87-0.99, respectively).

When the trials were analyzed individually, family history of type 1 diabetes played a significant role in the univariate

Table 1. Prevention trial characteristics

TrialNet protocol no.	Eligible population		IP and IP route	Length of participation	No. visits within year 1	Randomization ratio	Trial status	ClinicalTrials.gov reg. no.
	type 1 diabetes stage	Age						
TN-07	1	3-45 y[a]	Oral insulin, oral	72 mo+	5	1:1 (T_x:placebo)	Closed, results published	NCT00419562
TN-10	2	≥ 8 y[b]	Teplizumab, IV infusion	72 mo+	20, including 14-d infusion	1:1 (T_x:placebo)	Closed, results published	NCT01030861
TN-18	1	≥ 6 y[c]	Abatacept, IV infusion		15, including 12 monthly infusions	1:1 (T_x:placebo)	In follow-up	NCT01773707
TN-20	1 and 2	3-45 y[d,e]	Oral insulin, oral	12 mo	11	1:1 (T_{x1}: T_{x2} [open label])	Closed	NCT02580877
TN-22	1	3-45 y	Hydroxychloroquine, oral	72 mo+	7	2:1 (T_x:placebo)	Recruiting	NCT03428945

Abbreviations: IP, investigational product; T_x, x treatment.
[a]Age inclusion stratified by family history: 3-45 years for participants with first-degree probands, 3-20 years for participants with second- or third-degree probands.
[b]Participants needed to be between the ages of 1 and 45 years at the time of enrollment into the TrialNet Pathway to Prevention study, and age ≥ 8 years at time of randomization into trial.
[c]Participants needed to be between the ages of 1 and 45 years at the time of enrollment into the TrialNet Pathway to Prevention study, and age ≥ 6 years at time of randomization into trial.
[d]Participants needed to be between the ages of 1 and 45 years at the time of enrollment into the TrialNet Pathway to Prevention study, and age ≥ 3 years at time of randomization into trial.
[e]Age inclusion stratified by type 1 diabetes stage: ≥ 3 years for stage 1 participants, 3-7 years for stage 2 participants.

analyses of trial screening for TN-07 and TN-22. In TN-07, eligible participants who had a parent with type 1 diabetes showed higher rates of trial screening compared with participants who did not have a parent with diabetes (OR, 1.35; 95% CI, 1.04-1.77). Participants with an offspring or sibling with type 1 diabetes showed lower rates of TN-07 screening compared with participants with other first-degree relatives as probands (OR, 0.36; 95% CI, 0.19-0.68, and OR, 0.74; 95% CI, 0.58-0.94, respectively). Similarly, in TN-22 participants who had an offspring with type 1 diabetes showed lower rates of screening compared to those without an offspring with diabetes (OR, 0.51; 95% CI, 0.33-0.80). Family history stayed significant in the multivariate analysis for TN-07; eligible participants who had an offspring or sibling with diabetes showed lower rates of screening compared with those with other first-degree relatives as probands (OR, 0.81; 95% CI, 0.68-0.96, and OR, 0.89; 95% CI, 0.81-0.97, respectively). Significance was not found for any other proband analyses across the TrialNet prevention trials.

Participant sex was found to be significantly associated with trial screening when the trials were grouped, with male participants being more likely to screen for all trials (univariate: OR, 1.18; 95% CI, 1.02-1.38, $P < 0.05$; multivariate: OR, 1.02; 95% CI, 1.00-1.05, $P < 0.05$) and for oral drug trials (univariate: OR, 1.21; 95% CI, 1.02-1.43, $P < 0.05$). When the trials were analyzed individually, participant sex was only significantly associated with screening in the TN-07 trial, with male sex participants being more likely to screen than female sex participants (univariate: OR, 1.41; 95% CI, 1.12-1.78, $P < 0.01$; multivariate: OR, 1.08; 95% CI, 1.02-1.15, $P < 0.05$).

Research Site Factors

Site-specific characteristics played a significant role in trial screening for all the TrialNet prevention trials. As an international network, TrialNet research site location was analyzed, and US sites were compared with international sites. International sites were significantly less likely to screen eligible participants than US sites in the univariate analyses looking at the studies together ($P < 0.001$), by investigational product administration route (both $P < 0.001$), and individually (all $P < 0.05$). In multivariate analyses, international sites were less likely to screen eligible participants than US sites when the studies were grouped as a whole and by investigational product administration route (all $P < 0.001$). When considered individually in multivariate analyses, international sites were less likely to screen eligible participants than US sites in TN-07 (OR, 0.90; 95% CI, 0.83-0.99), TN-10 (OR, 0.94; 95% CI, 0.89-0.98), TN-18 (OR, 0.91; 95% CI, 0.86-0.97), and TN-22 (OR, 0.84; 95% CI, 0.79-0.89).

As a factor indicative of TrialNet engagement and site volume, research sites completing ≥140 annual PTP monitoring visits were compared with those completing <140 annual PTP monitoring visits. In univariate analyses, sites completing ≥140 annual PTP monitoring visits were more likely to screen eligible participants into trials than sites completing < 140 annual monitoring visits when the trials were grouped (univariate: OR, 1.34; 95% CI, 1.14-1.59; multivariate: OR, 1.04; 95% CI, 1.01-1.07), in the oral drug trials (univariate: OR, 1.72; 95% CI, 1.40-2.10; multivariate: OR, 1.09; 95% CI, 1.04-1.13), and in the intravenous infusion trials (univariate: OR, 1.69; 95% CI, 1.33-2.14). When analyzed individually, sites completing ≥140 annual PTP monitoring visits were

Table 2. Key participant and research site characteristics, by prevention trial

Variable	TN-07		TN-10		TN-18		TN-20		TN-22	
	eligible	Screened	eligible	Screened	eligible	Screened	eligible	Screened	eligible	Screened
N	1172	584 (49.8%)	1249	106 (8.5%)	1285	313 (24.4%)	667	113 (16.9%)	1336	371 (27.8%)
Sex[a]										
Female	507 (43.4%)	229 (39.2%)	597 (47.8%)	52 (49.1%)	647 (50.4%)	162 (51.8%)	268 (40.2%)	49 (43.4%)	614 (46.0%)	158 (42.6%)
Male	661 (56.6%)	355 (60.8%)	652 (52.2%)	54 (50.9%)	638 (49.7%)	151 (48.2%)	399 (59.8%)	64 (56.6%)	722 (54.0%)	213 (57.4%)
Race[a]										
Non-Hispanic White	930 (86.4%)	484 (88.0%)	1008 (88.0%)	97 (94.2%)	1059 (89.6%)	255 (86.7%)	531 (85.7%)	92 (85.2%)	1065 (87.2%)	298 (85.9%)
Hispanic White	78 (7.3%)	39 (7.1%)	85 (7.4%)	3 (2.9%)	65 (5.5%)	23 (7.8%)	46 (7.4%)	7 (6.5%)	75 (6.1%)	27 (7.8%)
Non-Hispanic Black	38 (3.5%)	13 (2.4%)	23 (2.0%)	0 (0.0%)	26 (2.2%)	6 (2.0%)	24 (3.9%)	6 (5.6%)	31 (2.5%)	7 (2.0%)
Hispanic Black	1 (0.1%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Non-Hispanic Other	28 (2.6%)	13 (2.4%)	27 (2.4%)	3 (2.9%)	32 (2.7%)	10 (3.4%)	18 (2.9%)	3 (2.8%)	49 (4.0%)	15 (4.3%)
Hispanic Other	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Relative with type 1 diabetes[a]										
Parent	289 (24.8%)	161 (27.6%)	326 (26.2%)	23 (21.7%)	325 (25.4%)	72 (23.0%)	183 (27.5%)	28 (24.8%)	372 (27.9%)	112 (30.4%)
Sibling	790 (67.7%)	376 (64.4%)	767 (61.6%)	69 (65.1%)	761 (59.4%)	193 (61.7%)	459 (68.9%)	79 (69.9%)	813 (61.0%)	223 (60.4%)
Offspring	51 (4.4%)	14 (2.4%)	171 (13.7%)	17 (16.0%)	213 (16.6%)	53 (16.9%)	26 (3.9%)	4 (3.5%)	150 (11.3%)	26 (7.1%)
2+ FDR	58 (5.0%)	29 (5.0%)	105 (8.4%)	9 (8.5%)	107 (8.4%)	23 (7.4%)	58 (8.7%)	7 (6.2%)	109 (8.2%)	27 (7.3%)
International site	185 (15.8%)	79 (13.5%)	207 (16.6%)	7 (6.6%)	305 (23.7%)	45 (14.4%)	134 (20.1%)	13 (11.5%)	266 (19.9%)	34 (9.2%)
Age at PTP screen	7.6 (4.6,11.6)	7.0 (4.3,10.5)	11.1 (7.6,16.5)	12.2 (9.5,16.7)	11.9 (7.7,18.6)	13.5 (8.7,22.3)	6.9 (4.2,10.6)	6.3 (3.6,9.6)	9.5 (5.8,14.5)	8.3 (4.8,12.2)
Age at multi-Ab[a]	8.2 (5.3,12.0)	7.5 (5.0,11.0)	11.6 (8.3,16.8)	12.9 (9.9,16.7)	12.7 (8.6,18.9)	13.9 (9.7,23.6)	7.7 (5.2,11.1)	7.1 (4.7,9.9)	10.3 (6.6,15.2)	9.0 (5.6,13.2)
Age at eligibility, y	8.9 (5.9,12.9)	8.1 (5.3,11.8)	13.3 (10.2,19.3)	13.6 (11.3,19.3)	14.5 (10.0,21.7)	15.1 (10.7,24.5)	9.9 (6.9,13.7)	8.3 (5.6,11.1)	13.1 (8.9,18.7)	11.0 (7.8,15.2)

Abbreviations: FDR, first-degree relative; multi-Ab, multiple autoantibody positive; PTP, TrialNet Pathway to Prevention study.
[a]Indicates some missing data.
For all non-age characteristics, the numbers in parentheses are percentages based on the N in the column. For the age characteristics, the numbers in parentheses are ranges.

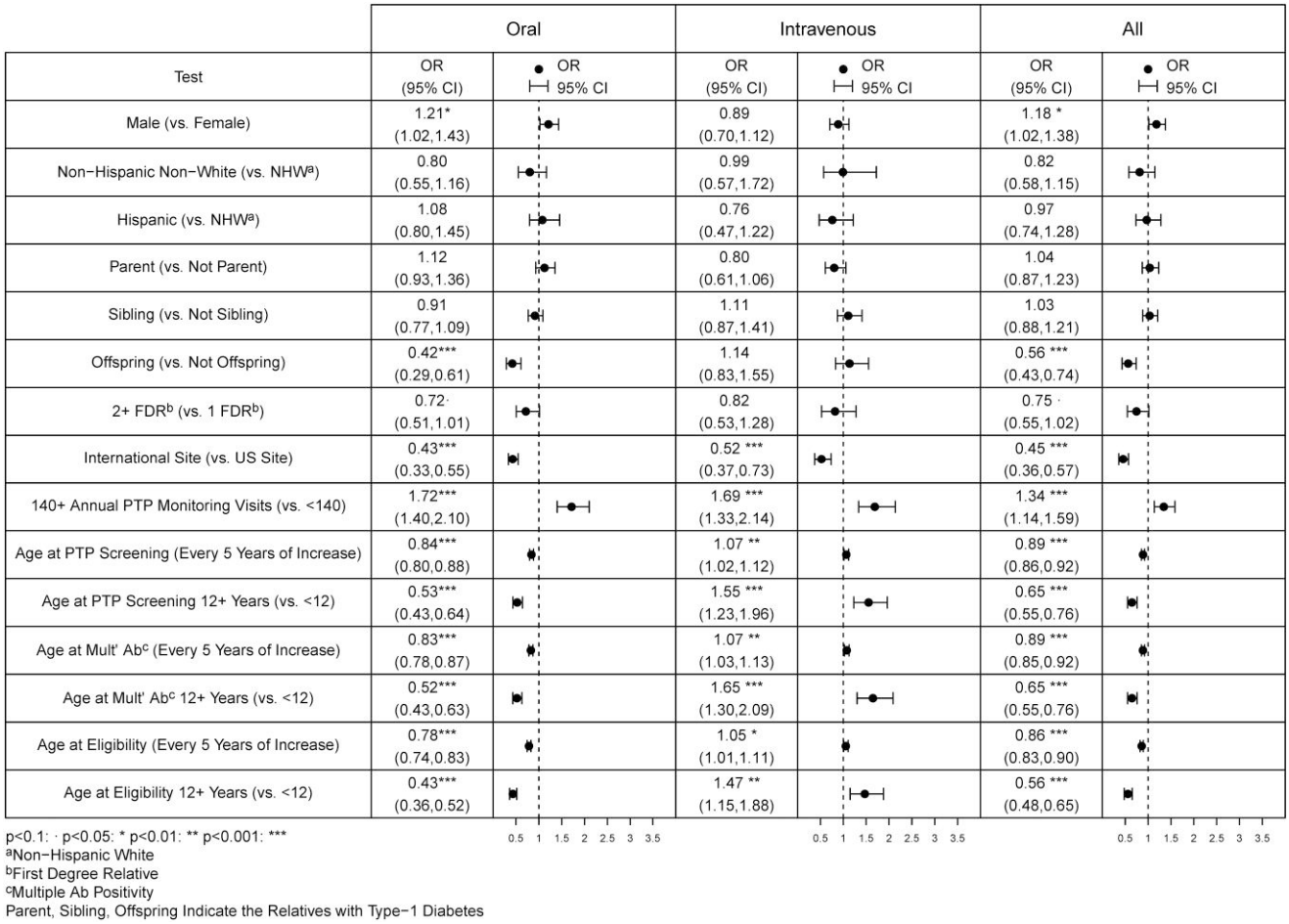

Figure 2. Univariate model results for factors on likelihood of trial screening, by investigational product administration route. Univariate analysis of potential factors associated with prevention trial screening in eligible participants by route of investigational product administration. To account for overlap in eligible participants across the studies over time, participant data were weighted by the number of studies for which they were eligible. Of participants eligible for the oral drug trials, screening rates were: 49.8% for TN-07 (584 screened/1172 eligible), 16.9% for TN-20 (113/667), and 27.8% for TN-22 (371/1336). Of participants eligible for the IV infusion trials, screening rates were: 8.5% for TN-10 (106/1249) and 24.4% for TN-18 (313/1285).

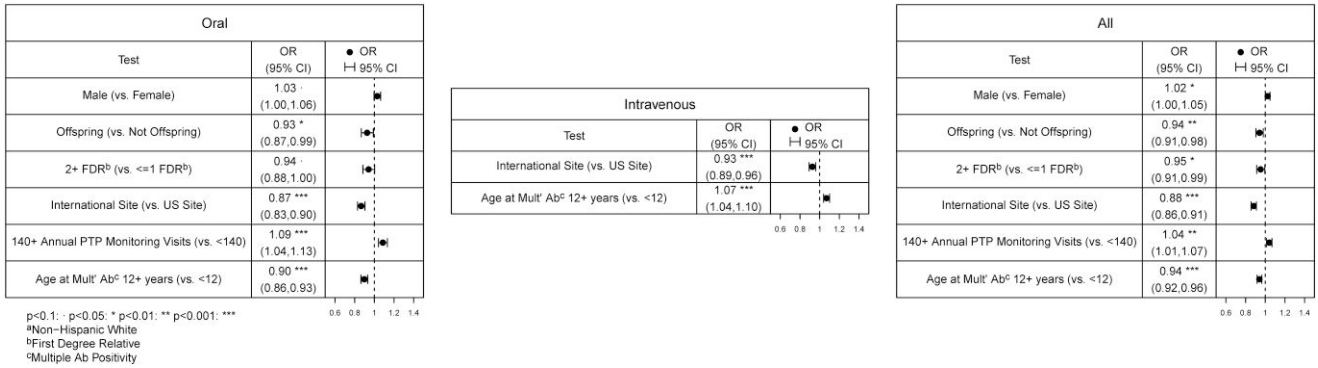

Figure 3. Multivariate model results for factors on likelihood of trial screening by investigational product administration route. Multivariate analysis of potential factors associated with prevention trial screening in eligible participants by route of investigational product administration. Factors with *P* values < 0.1 in univariate analyses were included in multivariate analyses. To account for overlap in eligible participants across the studies over time, participant data were weighted by the number of studies for which they were eligible. As the different age variables are closely correlated, only age at multiple Ab positivity was included as a categorical variable in the multivariate analyses.

more likely to screen eligible participants into TN-07 (OR, 1.36; 95% CI, 1.04-1.78), TN-18 (OR, 1.33; 95% CI, 1.03-1.72), TN-20 (OR, 2.44; 95% CI, 1.53-3.88), and TN-22 (OR, 1.51; 95% CI, 1.12-2.03) than those completing fewer than 140 annual monitoring visits. In multivariate analysis, research sites completing ≥140 annual PTP monitoring

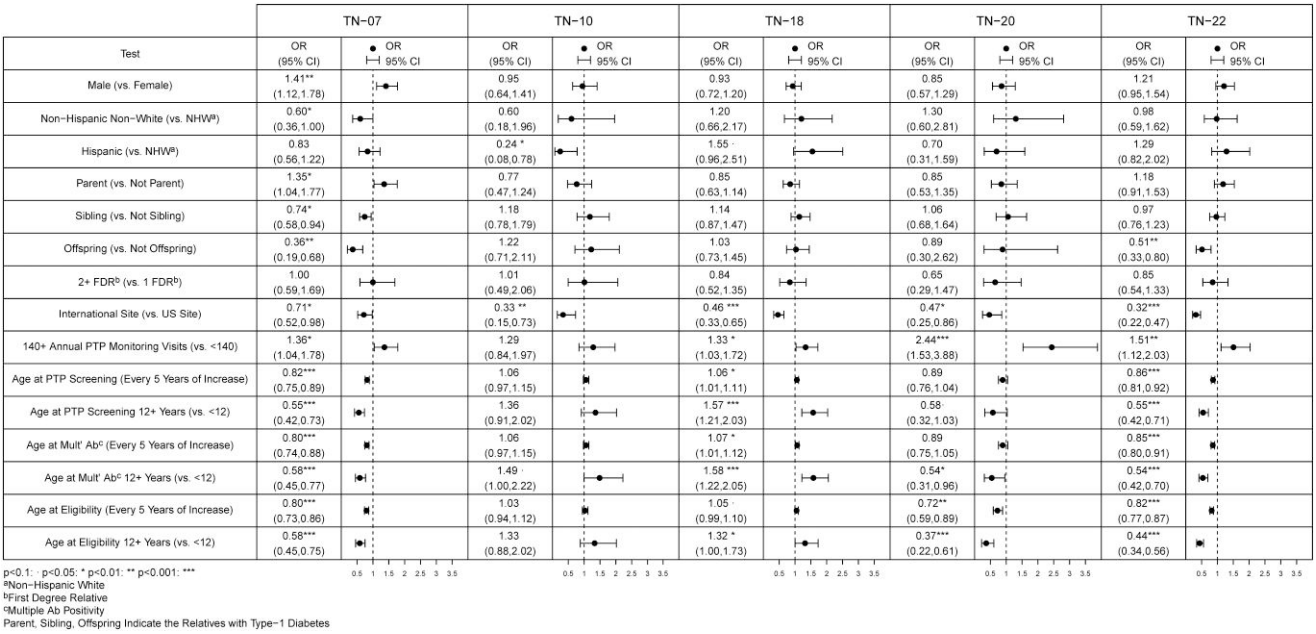

Figure 4. Univariate model results for factors on likelihood of trial screening by trial. Univariate analysis of potential factors associated with trial screening in eligible participants by prevention trial. Of participants eligible for each prevention trial, screening rates were: 49.8% for TN-07 (584 screened/1172 eligible), 8.5% for TN-10 (106/1249), 24.4% for TN-18 (313/1285), 16.9% for TN-20 (113/667), and 27.8% for TN-22 (371/1336).

visits were more likely to screen eligible participants into the TN-20 trial (OR, 1.13; 95% CI, 1.05-1.22) than research sites completing fewer than 140 annual PTP monitoring visits.

Discussion

To our knowledge, this is the first study to analyze potential factors influencing screening for type 1 diabetes prevention trials. A previous analysis of the TrialNet PTP study revealed significant differences between Ab-positive participants who enrolled in the monitoring phase of the study and those who did not transition into monitoring [24]. Despite having an opportunity to be monitored for disease progression, 34% of multiple Ab-positive participants at high risk of disease progression at screening did not enroll into the OGTT monitoring phase of the PTP study [24]. Although the study confirmed clear differences between participants successfully enrolled in the monitoring phase of the PTP study and those lost to follow-up after screening for islet autoantibodies, it did not evaluate enrollment into any TrialNet drug prevention trials. The intent of this study was to expand upon the findings of the Sims et al study and evaluate potential facilitators contributing to enrollment into a prevention study from a monitoring study. Understanding these factors is especially important because drug development is reliant on clinical trial enrollment.

This study found that participant age, sex, and relationship to proband are significant factors associated with TrialNet prevention trial screening. In addition, site-specific factors, including site activity in the PTP study and site location, were associated with screening for prevention trials. Overall, screening was highest for the prevention trials evaluating oral drugs (oral insulin and hydroxychloroquine) compared with more intensive trials with IV infusions (abatacept and teplizumab).

Age was a significant factor affecting screening into prevention trials, with younger participants being more likely to screen overall and for the oral drug trials (TN-07, TN-20, and TN-22) when evaluated together and individually. In contrast, age ≥12 years was associated with screening for the IV infusion trials and for TN-18 individually. No association was seen between age and screening for the TN-10 trial, but this may be a result of the small sample size, which is a limitation in the TN-10 analysis.

The differences in age association between the oral study drug trials and TN-18 is likely because of parental involvement in the decision to screen for the trial, assumed risk for disease progression, and trial characteristics. The TN-07, TN-20, and TN-22 trials enrolled participants as young as 3 years old, whereas the TN-10 and TN-18 trials involved investigational products needing IV infusions and required participants be 8 years old and 6 years old, respectively. In addition to the route of investigational product administration, perceived burden of participation, and differences in age eligibility, it is likely that other trial characteristics confounded the age analyses. For example, the TN-07, TN-20, and TN-22 trials had fewer visits in the first year of trial participation, which may have been more appealing to families with younger participants.

Participants with an offspring with type 1 diabetes showed lower rates of screening for all trials and oral drug trials compared with participants with other first-degree relatives as probands. In TN-07, we also found that participants with a parent with type 1 diabetes were significantly more likely to screen compared with participants without a parent with type 1 diabetes. Potential explanations include differences in risk perception and inclination, with parents having a strong motivation to prevent diagnoses in their offspring without type 1 diabetes because they are directly aware of the burden and long-term complications of the disease [1–5]. Although siblings represent the largest category of relatives in the PTP study and prevention trials (around 60%-70%), we found that participants with sibling probands were less likely to

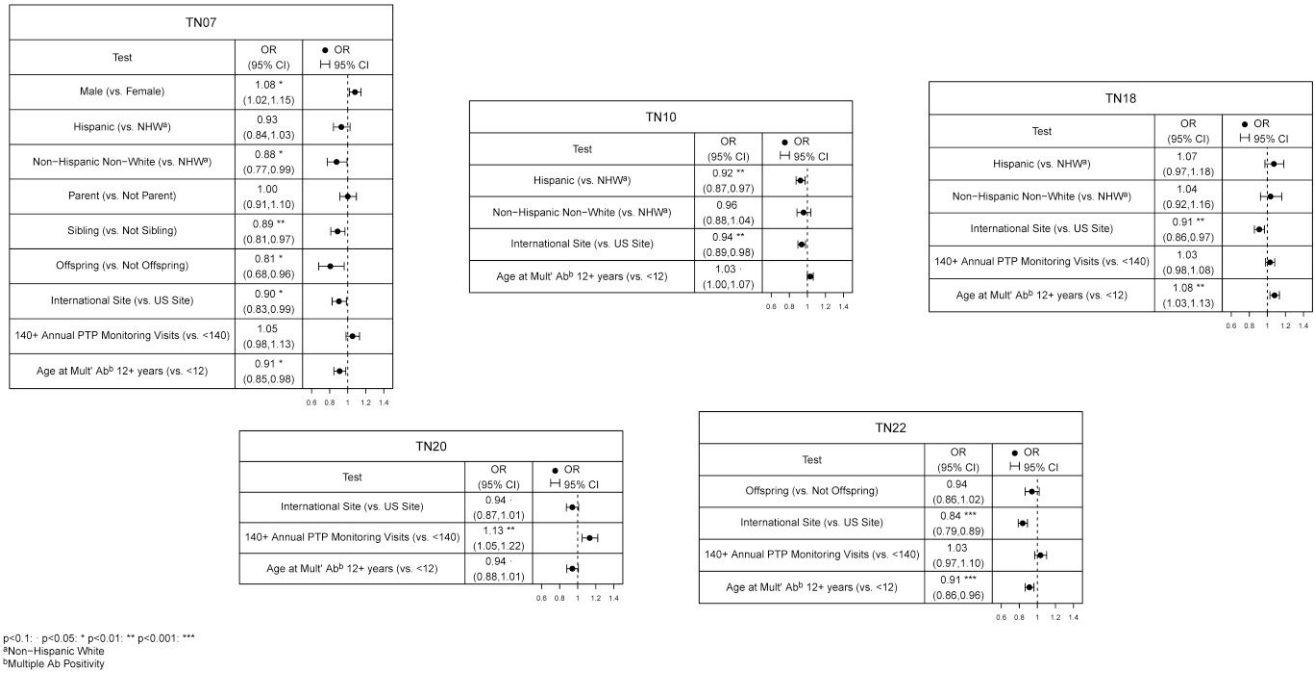

Figure 5. Multivariate model results for factors on likelihood of trial screening by trial. Multivariate analysis of potential factors associated with trial screening in eligible participants, by prevention trial. Factors with *P* values < 0.1 in univariate analyses were included in multivariate analyses. Because the different age variables are closely correlated, only age at multiple Ab positivity was included as a categorical variable in the multivariate analyses.

screen for TN-07 compared with participants with other first-degree relatives as probands. It is likely that this finding may have been confounded by participants' age and affected by the volume of siblings within the TrialNet studies.

Site-specific factors associated with screening into prevention trials included site monitoring volume and location, with international sites being less likely to screen eligible monitoring participants into prevention trials compared with US sites. Sites completing ≥ 140 annual PTP monitoring visits were more likely to screen eligible participants overall, in the oral drug trials and in the IV infusion trials. Recruiting prevention trials are commonly discussed at PTP monitoring visits and when PTP monitoring results are shared with participants. Additionally, sites with higher volumes of PTP monitoring likely have the consistent clinical research infrastructure and team needed to conduct these types of clinical trials, highlighting the importance of established and experienced centers for clinical interventions. Because TrialNet clinical trials are typically first reviewed by the US Food and Drug Administration, the lower screening into prevention trials at international sites was likely from delayed approval of specific clinical trials outside the United States by other regulatory agencies and ethic committees, the lack of a central IRB, and delays receiving investigational products. Together, these factors resulted in delayed trial initiation and shorter accrual periods.

Despite the wide reach of Type 1 Diabetes TrialNet, the prevention trials included in this study experience the same barriers to clinical trial enrollment seen in other diseases, specifically in diversity and inclusion [19, 25]. The PTP monitoring population itself is weighted toward White and non-Hispanic participants, with 86% to 90% of trial-eligible participants being NHW and minorities being underrepresented. As a persisting and important issue, more effort must be placed on reaching those identifying as ethnic or racial minorities. TrialNet is allocating additional resources to recruitment initiatives with the goal of establishing key relationships and reaching underrepresented communities. TrialNet has shown very high retention rates of 92% to 98% for both prevention and intervention trials; similar retention rates may be seen for minority participants once the appropriate steps are taken to increase recruitment.

Other limitations of this study include various accrual periods, different eligibility trial criteria (such as age), and investigational product administration route. Before the TrialNet transition to central IRB oversight, site accrual periods varied and did not necessarily match the study-wide accrual periods. Although prevention trial eligibility was based on retrospective PTP data review, eligibility was potentially restricted by a participant's proximity to an enrolling TrialNet site. Thus, delays in site activation, caused by delays in regulatory or IRB/ethics committee approval, could affect prevention trial enrollment. In addition, although key protocol changes were implemented to mitigate the impact of the pandemic, such as remote visits and utilization of third-party laboratories, TN-22 enrollment was affected by the COVID-19 pandemic.

The results of this study provide us with important information for planning future prevention trials and creating recruitment strategies. Beyond what our analyses show, we can assume that key clinical trial factors influence a participant's decision to screen for trial inclusion, such as those seen in oncology trials involving adult and adolescent participants [19, 25–27]. Increasing clinical trial enrollment will likely require a 2-pronged approach. First, sites must ensure that trials are promoted by qualified research personnel and accessible to all eligible participants. TrialNet research sites need to stay engaged and involved in monitoring, and additional resources should be available to ensure minority groups are reached

and identified when eligible. Second, we need to design clinical trials with the participant and family at the forefront of the protocol. When permitted by investigational treatment and subsequent safety oversight, additional efforts should be made to maximize potential benefits to the participant while reducing participant burden. Qualitative, subjective input may be the key for understanding why participants and families elect to screen for prevention trials and what factors are most influential when they decide not to screen for prevention trials. Understanding the factors associated with enrollment in prevention trials allows researchers to develop proactive strategies to shorten the time it takes to enroll into trials and increase the likelihood of individual engagement, ultimately expediting clinical trial prevention for type 1 diabetes.

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Author Contributions

M.K. planned analyses, interpreted data, and wrote the manuscript. L.Y. planned analyses, evaluated, and interpreted data, and edited the manuscript. E.K.S., D.W., D.S., S.L., J.K., W.E.R., P.A.G., I.L., J.B., L.A.D., and K.C.H. interpreted data and edited the manuscript. A.K.S. planned analyses, interpreted data, and wrote and edited the manuscript. All authors read and approved the final version. M.K. and A.K.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

The authors have no relevant conflict of interest to disclose.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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