The Clinical Impact of Teplizumab on Delaying Progression to Stage 3 Type 1 Diabetes: A Multi-Dimensional Analysis of Efficacy, Immunological Mechanisms, and Healthcare Delivery

Introduction to pre-symptomatic disease staging and therapeutic paradigm shifts

Type 1 diabetes mellitus is a chronic, progressive endocrine and metabolic disorder caused by the autoimmune destruction of insulin-producing pancreatic beta cells.[1] Historically, clinical intervention was entirely reactive, initiating with lifelong exogenous insulin replacement therapy only after the emergence of clinical symptoms.[3] Over the last two decades, the tracking of longitudinal cohorts has redefined the natural history of type 1 diabetes as a predictable, three-stage clinical continuum.[1] Stage 1 represents the onset of beta-cell autoimmunity, defined by the presence of two or more islet-related autoantibodies in individuals who remain normoglycemic and asymptomatic.[1] Stage 2 is characterized by persistent autoimmunity and the development of dysglycemia—impaired glucose tolerance or impaired fasting glucose—without overt symptoms.[3] Once an individual progresses to Stage 2, the lifetime risk of developing symptomatic, insulin-dependent Stage 3 disease is virtually 100%.[1]

The licensing of teplizumab, a humanized anti-CD3 monoclonal antibody, represents a historic milestone, shifting the therapeutic paradigm from reactive hormonal replacement to active, disease-modifying immunotherapy.[5] Teplizumab targets the autoimmune process during the pre-symptomatic phase, preserving residual beta-cell functional mass and delaying the onset of insulin dependence.[9] This report evaluates the quantitative clinical efficacy, underlying molecular mechanisms, metabolic trajectories, and systemic implementation challenges of teplizumab therapy in non-diabetic individuals with Stage 2 type 1 diabetes.

Efficacy of teplizumab: clinical delay to stage 3 disease onset

The regulatory approvals of teplizumab are based on the Phase 2, randomized, double-blind, placebo-controlled, event-driven TrialNet TN-10 trial (NCT01030861).[1] This landmark study randomized 76 non-diabetic, high-risk relatives of type 1 diabetes patients who met the criteria for Stage 2 disease.[8] Eligible participants possessed two or more autoantibodies—including glutamic acid decarboxylase 65 (GAD65), insulin autoantibodies (IAA), insulinoma-associated antigen 2 (IA-2A), zinc transporter 8 (ZnT8A), or islet cell autoantibodies (ICA)—and

demonstrated dysglycemia on an oral glucose tolerance test.[1] The trial cohort had a median age of 13 years, with 72% of participants aged 18 years or younger.[14] Participants were randomized in a 1:1 ratio to receive either a single 14-day intravenous course of teplizumab ($N = 44$) or placebo ($N = 32$).[8]
The primary clinical endpoint was the time from randomization to the diagnosis of clinical Stage 3 type 1 diabetes.[1] Efficacy data have been reported across three major analytical intervals, reflecting the evolving maturity of the trial data.

The initial trial publication and regulatory data cuts

The initial analysis published in 2019, which utilized a median follow-up of 745 days, demonstrated that a single 14-day course of teplizumab delayed progression to clinical type 1 diabetes by a median of 24 months compared to placebo.[9] The median time to diagnosis was 48.4 months in the teplizumab group compared to 24.4 months in the placebo group.[14] In this academic data cut, Stage 3 disease was diagnosed in 43% of the teplizumab cohort versus 72% of the placebo cohort, yielding a hazard ratio of 0.41 (95% CI: 0.22 to 0.78; $P = 0.006$ by an adjusted Cox proportional-hazards model).[14]
A slightly adjusted regulatory data cut, presented in the manufacturer's licensing dossiers for the FDA and Health Canada, reported a median time to diagnosis of 49.5 months for the teplizumab cohort compared to 24.9 months for the placebo group.[12] This configuration yielded an absolute median delay of 24.6 months (Hazard Ratio $= 0.41$; 95% CI: 0.22 to 0.78; $P =$).[9]

Extended cohort and long-term follow-up analyses

In 2021, Sims and colleagues published an extended follow-up analysis with a median monitoring duration of 923 days (range: 74 to 3,119 days).[13] With this additional follow-up, the median time to Stage 3 diagnosis was 59.6 months in the teplizumab group versus 27.1 months in the placebo group, representing an absolute delay of 32.5 months (approximately 2.7 years).[13] Over this extended period, 50% of teplizumab-treated participants remained entirely diabetes-free compared to 22% of placebo-treated controls ($\text{adjusted HR} = 0.457$; $P =$).[13]
A subsequent long-term analysis published in 2024 by Lledó-Delgado and colleagues monitored the TN-10 cohort over a median follow-up of 80.46 months.[9] This analysis demonstrated a median time to Stage 3 onset of 52.2 months (95% CI: 30.5 to 86.7) in the teplizumab cohort versus 27.3 months (95% CI: 9.5 to 48.4) in the placebo group, showing a sustained delay of 24.9 months ($P =$ by log-rank test).[9] At the final censoring point, 36% of teplizumab-treated patients remained undiagnosed with Stage 3 disease, compared to

12.5% in the placebo arm ($P = 0.03$ by Fisher's exact test).[24]

Table 1 summarizes these clinical efficacy metrics across the successive data cuts.

Table 1: Efficacy outcomes and clinical delay across TN-10 analyses

Efficacy Parameter	Initial Academic Cut (Herold et al., 2019)	Regulatory Approval Dossier Cut	Extended Follow-Up Cut (Sims et al., 2021)	Long-Term Repertoire Cut (Lledó-Delgado et al., 2024)
Median Follow-Up Duration	745 days (24.5 months) [9]	Teplizumab: 27.5 mos; Placebo: 17.8 mos [21]	923 days (30.3 months) [22]	80.46 months (6.7 years) [9]
Teplizumab Onset Median	48.4 months [14]	49.5 months (95% CI: 32.2 to NE) [21]	59.6 months [22]	52.2 months (95% CI: 30.5 to 86.7) [24]
Placebo Onset Median	24.4 months [14]	24.9 months (95% CI: 9.5 to 48.6) [21]	27.1 months [22]	27.3 months (95% CI: 9.5 to 48.4) [24]
Absolute Median Progression Delay	**24.0 months** [9]	**24.6 months** [21]	**32.5 months** [13]	**24.9 months** [25]
Progression Hazard Ratio (HR)	0.41 (95% CI: 0.22 to 0.78) [14]	0.41 (95% CI: 0.22 to 0.78) [12]	0.457 [13]	Not reported directly in text [24]; ($P =$ log-rank) [24]
Statistical Significance	$P = 0.006$ [14]	$P =$ [9]	$P =$ [13]	$P =$ [24]
Proportion	43% (19/44)	45% (20/44)	50% (22/44)	64% (28/44)

Diagnosed with Stage 3	teplizumab vs. 72% (23/32) placebo [14]	teplizumab vs. 72% (23/32) placebo [9]	teplizumab vs. 78% (25/32) placebo [22]	teplizumab vs. 87.5% (28/32) placebo [24]
Progression-Free Survival Rate	57% of active group [29]	Not specified	50% teplizumab vs. 22% placebo [22]	36% teplizumab vs. 12.5% placebo [24]

Heterogeneity of clinical efficacy and predictive biomarkers

Although a single course of teplizumab demonstrates clear efficacy in delaying the onset of Stage 3 type 1 diabetes, there is significant clinical heterogeneity in patient responses.[10] Long-term follow-up has revealed that while some individuals progress to Stage 3 within 6.5 months of treatment, others remain completely diabetes-free for over 10 years.[25] Subgroup and biomarker analyses of the TN-10 cohort have identified several genetic, immunological, and metabolic baselines that predict a more favorable response to teplizumab.

Genetic HLA genotypes and autoantibody profiles

- **HLA-DR4 Positivity:** The presence of the Human Leukocyte Antigen (HLA) class II allele HLA-DR4 was strongly associated with enhanced teplizumab efficacy, demonstrating a significant reduction in the hazard of progression to clinical disease ($\mathrm{HR} = 0.20$; 95% CI: 0.09 to 0.45).[31]
- **HLA-DR3 Negativity:** Conversely, individuals who were HLA-DR3-negative exhibited a more robust response to teplizumab compared to placebo, yielding an HR of 0.18 (95% CI: 0.07 to 0.45).[31]
- **Anti-Zinc Transporter 8 (ZnT8) Negativity:** Participants who tested negative for the anti-ZnT8 autoantibody at baseline showed a strong response to therapy, with an adjusted HR of 0.07.[31]

Baseline metabolic status

The metabolic state of the prediabetic individual at the time of drug administration is also a powerful determinant of therapeutic response.[22] Participants with a baseline C-peptide response to an oral glucose tolerance test (OGTT) below $1.75\ \mathrm{nmol/L}$ derived the greatest benefit from teplizumab ($\mathrm{HR} = 0.19$; 95% CI: 0.08 to 0.47).[31] This finding suggests that teplizumab is most effective when administered during a window of active, immune-mediated beta-cell destruction, rather than a quiescent prediabetic phase.[22]

Furthermore, a retrospective study comparing the TN-10 placebo group ($n = 32$) with the German Fr1da Bavarian cohort ($n = 152$) of screen-detected Stage 2 children demonstrated that the rate of disease progression is similar regardless of family history.[30] This analysis validates that disease progression is driven by autoantibody load and metabolic dysregulation rather than familial relation, confirming that the preventive benefits of teplizumab are fully generalizable to screen-detected prediabetic populations in the general public.[32]

Table 2: Baseline progression risk: TN-10 placebo vs. Fr1da Bavarian cohort

Parameter	TN-10 Placebo Cohort (n=32)	Fr1da Bavarian Cohort (n=152)	Statistical Comparison
Familial Status	100% First-Degree Relatives (FDRs) [32]	Screen-detected general population [32]	Not applicable
Median Time to Stage 3 Onset	24.4 months [32]	Approximately 24 months [32]	No significant difference [32]
Unadjusted Hazard Ratio (HR)	1.0 (Reference)	1.3 (95% CI: 0.8 to 2.1) vs. TN-10 placebo [32]	$P >$ (Non-significant) [32]
Adjusted HR (Covariates)	1.0 (Reference)	1.1 (Adjusted for anti-IA-2, baseline $HbA1c$, and glucose) [32]	$P >$ (Non-significant) [32]
Clinical Implication	Natural history of Stage 2 T1D is driven by metabolic/islet autoantibody load [32]	Teplizumab trial data can be generalized to public screening cohorts [32]	Validates pan-European and global general public screening programs [32]

Cellular and molecular mechanisms of operational tolerance

Teplizumab is an Fc receptor-nonbinding humanized anti-CD3 monoclonal antibody derived

from the murine OKT3 clone.[14] Historically, clinical use of OKT3 was limited by severe cytokine release syndrome (CRS) caused by cross-linking between CD3 molecules on T cells and Fcγ receptors on accessory cells.[1] Teplizumab incorporates a mutated human IgG1 Fc region containing two amino acid substitutions—leucine-to-alanine mutations at residues 234 and 235 (the "ala-ala" configuration)—which prevent Fcγ receptor binding while retaining target affinity.[1] Consequently, the antibody delivers a weak, partial agonist signal through the T-cell receptor (TCR) complex, avoiding massive systemic cytokine release while inducing a state of durable immune modulation.[19]

T-cell phenotype reprogramming and regulatory induction

The partial agonistic signal delivered by teplizumab induces several downstream changes in the T-cell compartment to alter the course of autoimmune disease [3]:

- **Effector Cell Anergy and Apoptosis:** Teplizumab deactivates or induces apoptosis in autoreactive, pathogenic CD8+ and CD4+ T lymphocytes that infiltrate the pancreatic islets to destroy insulin-producing beta cells.[3]
- **Regulatory T-cell (Treg) Promotion:** Simultaneously, the drug promotes the generation and suppressive function of $CD4^{+}FoxP3^{+}$ regulatory T cells and Tregs in peripheral blood.[3] These cells help restore immune homeostasis by suppressing pro-inflammatory cytokine secretion (including IL-2 and IFN-γ) and releasing anti-inflammatory cytokines, such as IL-4 and IL-10.[3]
- **Phenotypic T-cell Exhaustion:** Teplizumab induces a transient, partial exhaustion phenotype in CD8+ memory T lymphocytes, characterized by cell-surface co-expression of the coinhibitory receptors KLRG1 and TIGIT.[14] These exhausted cells exhibit a reduced capacity to secrete the pathogenic cytokines TNF-α and IFN-γ.[22] This signature peaks around 6 months post-treatment and declines toward baseline by 12 to 18 months.[25]

Transcriptomic profiling of responders vs. non-responders

Single-cell RNA sequencing of peripheral blood lymphocytes from the TN-10 trial has identified distinct transcriptomic signatures that distinguish clinical responders (defined as remaining diabetes-free for $\geq 60 \text{ months}$; $n = 17$) from non-responders ($n = 27$)[24]:

- **TCR Pathway Down-regulation:** At 3 months post-infusion, both groups show transcriptional signatures of T-cell activation.[26] However, by 18 months, clinical responders show down-regulation of genes in T-cell receptor signaling and activation pathways.[26]
- **CD8+ and CD4+ Dynamics:** Responders demonstrate a significant relative increase in the percentage of CD4+ T cells at 6 months ($P < 0.05$), an increase in CD8+ T cells at 3 months ($P < 0.01$), and a transient decrease in the CD4+ to CD8+ ratio at 3 months

($P < 0.01$).[24]

- **IL-7 Receptor (CD127) Down-regulation:** Teplizumab reduces the expression of the IL-7 receptor alpha chain ($IL7R$ or $CD127$) on CD8+ memory T cells, which is required for their homeostatic survival and expansion.[24] Lower expression of $CD127$ restricts the replenishment of autoreactive T-cell clones, directly correlating with prolonged diabetes-free survival intervals.[24]
- **Abolishing Islet Clonal Expansion:** In placebo-treated individuals, the frequency of islet antigen-reactive CD8+ T cells progressively expands over time.[24] Teplizumab completely prevents this expansion, stabilizing the autoreactive TCR repertoire.[24]

Metabolic trajectories and beta-cell preservation

The transition from Stage 2 pre-symptomatic dysglycemia to clinical Stage 3 type 1 diabetes is characterized by a rapid, precipitous decline in beta-cell function and insulin secretion, typically accelerating in the 6 months immediately preceding diagnosis.[22] Teplizumab modulates this metabolic decline, preserving beta-cell functional mass over a prolonged period.

C-peptide trajectories and preservation

C-peptide is a well-established surrogate marker of clinical beta-cell function, secreted in equimolar concentrations with endogenous insulin.[37] In placebo-treated Stage 2 patients, C-peptide levels decline progressively over time.[15] Teplizumab treatment reverses this decline, stabilizing the C-peptide area under the curve (AUC) during oral glucose tolerance testing.[15] In the Sims et al. 2021 analysis, teplizumab-treated individuals maintained a significantly higher average on-study C-peptide AUC compared to placebo controls ($1.94\ \mathrm{pmol/mL}$ vs. $1.72\ \mathrm{pmol/mL}$; $P = 0.006$).[15]

Oral Minimal Model (OMM) and beta-cell glucose sensitivity

Post-hoc analyses of the TN-10 dataset using the Oral Minimal Model (OMM) have characterized the metabolic dynamics following teplizumab treatment [30]:

- **Total Insulin Secretion (Φ_{total}):** Over 12 months, OMM-estimated insulin secretion progressively declined in the placebo group but rose significantly in the teplizumab-treated group.[30]
- **Early-Phase Insulin Secretion:** Teplizumab-treated individuals showed marked improvements in early-phase insulin secretion and total insulin secretion, representing a preservation of beta-cell glucose sensitivity.[22]
- **Progressor Status Dynamics:** Teplizumab-treated "slow-progressors" (those remaining diabetes-free for $> 2\ \mathrm{years}$) maintained elevated insulin secretion and exhibited a significant reduction in endogenous insulin clearance, which acts as a compensatory

physiological mechanism to sustain peripheral insulin concentrations.[30]

- **Early Marker of Treatment Failure:** A decline of $> 25\%$ in OMM-estimated insulin secretion at 3 months post-infusion served as a highly specific predictor of rapid progression to Stage 3 disease within 2 years, demonstrating a specificity of 0.95 (95% CI: 0.86 to 1.00) and a correct classification rate of 92%.[30]

Safety, tolerability, and clinical administration configurations

The clinical use of teplizumab requires a careful balance between immunomodulatory efficacy and manageable, transient side effects.[9] Safety data from the TN-10 study and broader pooled safety databases ($N = 773$) show that adverse events are predictable, transient, and self-limiting, occurring primarily during the 14-day administration course.[12]

Adverse events and safety parameters

- **Lymphopenia:** Transient lymphopenia occurs in 73% of teplizumab-treated individuals compared to 6% of placebo controls.[12] The lymphocyte count declines during the first week of administration, but lymphocyte levels begin to recover after the fifth day of treatment, returning to baseline values within two weeks after treatment completion (and fully resolving by Week 6) without causing long-term immunosuppression.[33]
- **Leukopenia and Neutropenia:** Leukopenia occurred in 21% of the teplizumab arm (versus 0% in placebo).[12] Severe neutropenia (Grade ≥ 3) is a recognized risk requiring hematologic monitoring.[4]
- **Cutaneous Rash:** A transient maculopapular, pruritic, or peeling rash occurs in 36% of active-treatment patients (versus 0% in placebo).[9] It typically resolves spontaneously without sequelae.[33]
- **Cytokine Release Syndrome (CRS):** Manifesting in approximately 2% of teplizumab-treated patients, mild-to-moderate CRS presents as pyrexia, headache (11%), nausea, fatigue, myalgia, arthralgia, and transient transaminase (ALT/AST) elevations.[9]

Clinical monitoring and mitigation protocols

To safely deliver the daily 14-day intravenous course, clinicians must implement strict monitoring and premedication protocols:

- **Premedication Protocol:** For the first five days of the infusion course, patients must receive premedications consisting of an antipyretic (acetaminophen/paracetamol), an antihistamine, and/or an antiemetic to mitigate CRS and infusion reactions.[9]
- **Hematologic and Hepatic Monitoring:** Baseline complete blood count (CBC) and liver function tests are mandatory.[19] Infusions must be withheld or permanently discontinued if a patient develops ALT or AST elevations > 5 times the upper limit of normal (ULN),

bilirubin > 3 times the ULN, or prolonged severe lymphopenia ($< 500\ \text{lymphocytes}/\mu\text{L}$ lasting 1 week or longer).[9]

- **Infection Screen:** Serious infections occurred in 9% of teplizumab-treated participants compared to 0% of those receiving placebo, all occurring more than two weeks after completing therapy.[31] Teplizumab is not recommended for patients with active serious infections, or those with laboratory evidence of acute EBV or CMV.[9]

Dosing variations across clinical protocols

The dosing configurations of teplizumab vary across clinical trials, commercial labels, and age groups.[1] Table 3 details these distinct dosing regimens.

Table 3: Comparative teplizumab dosing regimens across clinical configurations

Parameter	Approved Commercial Labeling (Tzield)	TN-10 Clinical Trial Protocol	NCT04270942 Open-Label Trial Protocol	PETITE-T1D (NCT05757713) Pediatric Protocol
Target Population	Adults and pediatric patients $\geq$ years with Stage 2 T1D [19]	Relatives $\geq$ years with Stage 2 T1D [1]	Relatives with new-onset T1D within 1 year [42]	Pediatric patients aged 1 to 8 years with Stage 2 T1D [35]
Treatment Duration	14 consecutive days [19]	14 consecutive days [1]	12 consecutive days [42]	14 consecutive days [35]
Day 1 Dose	$65\ \mu\text{g}/\text{m}^2$ [19]	$51\ \mu\text{g}/\text{m}^2$ (Designated Day 0) [1]	$106\ \mu\text{g}/\text{m}^2$ [42]	Clinically adjusted pediatric dosing [35]
Day 2 Dose	$125\ \mu\text{g}/\text{m}^2$ [19]	$103\ \mu\text{g}/\text{m}^2$ (Designated Day 1) [17]	$425\ \mu\text{g}/\text{m}^2$ [42]	Clinically adjusted pediatric dosing [35]

Day 3 Dose	$250\ \mu g/m^2$ [19]	$207\ \mu g/m^2$ (Designated Day 2) [1]	$850\ \mu g/m^2$ [42]	Clinically adjusted pediatric dosing [35]
Day 4 Dose	$500\ \mu g/m^2$ [19]	$413\ \mu g/m^2$ (Designated Day 3) [1]	$850\ \mu g/m^2$ [42]	Clinically adjusted pediatric dosing [35]
Days 5–14 Dose	$1,030\ \mu g/m^2$ daily [19]	$826\ \mu g/m^2$ daily (Days 4–13) [1]	$850\ \mu g/m^2$ daily (Days 3–12) [42]	Clinically adjusted pediatric dosing [35]
Infusion Duration	Minimum of 30 minutes [19]	Approximately 30 minutes [1]	Daily IV infusion [42]	**2-hour infusions** due to peak concentration pharmacokinetic profile [35]
Cumulative Dose	Approximately $11.2\ mg/m^2$	Approximately $9.1\ mg/m^2$	Approximately $9.0\ mg/m^2$ [42]	Tailored to pediatric pharmacokinetics [35]

Healthcare system implementation and economic considerations

The regulatory approval of teplizumab marks a historical milestone, representing the first disease-modifying therapy capable of altering the natural course of pre-symptomatic type 1 diabetes.[5] Following its initial US FDA approval in November 2022 for adults and children aged 8 years and older, the therapeutic landscape has expanded globally.[12] Health Canada issued priority approval in May 2025, and the European Commission granted approval in January 2026.[8]

In a significant clinical advancement, the FDA expanded teplizumab's approval in April 2026 to include pediatric patients as young as 1 year of age, supported by the safety and pharmacokinetic findings of the Phase 4 PETITE-T1D trial.[35]

The diagnostic screening bottleneck

Despite these clinical advancements, widespread utilization of teplizumab is restricted by a

major diagnostic bottleneck.[2] Because Stage 1 and Stage 2 type 1 diabetes are entirely asymptomatic, patients are not routinely identified in daily clinical practice.[4] Widespread autoantibody and glycemic screening are currently absent from national healthcare systems.[2] Most eligible individuals are identified incidentally or through specialized research studies, such as the ELSA study (UK) or the Fr1da study (Germany).[4] To maximize the public health benefit of teplizumab, clinical experts advocate for the establishment of structured, population-wide pediatric screening programs.[2]

Health Technology Assessment and Economic Trade-offs

Health technology assessment agencies, including the National Institute for Health and Care Excellence (NICE) in the UK and the High Health Authority (HAS) in France, have expressed economic caution.[4] While HAS deemed the clinical utility of teplizumab "Important," NICE's draft guidance deferred routine reimbursement, citing economic model uncertainties regarding the exact eligible population and the precise long-term quality of life (QALY) impacts.[4]
Economically, teplizumab affects the healthcare system through several competing variables:

- **Negative Cost Factors:** High upfront drug acquisition costs, the clinical infrastructure required to deliver 14 consecutive daily infusions, and the medical management of transient adverse events (specifically lab monitoring and CRS mitigation).[4]
- **Positive Cost Factors:** Prolonged avoidance of expensive exogenous insulin therapy, fewer acute clinical emergencies at diagnosis—such as diabetic ketoacidosis (DKA)—and a projected reduction in long-term diabetic microvascular and macrovascular complications.[2]
- **Quality of Life Impacts:** Delaying the onset of symptomatic disease by an average of 2 to 3 years improves health-related quality of life (HRQoL) and psychosocial outcomes, particularly for children and adolescents navigating critical developmental milestones.[2] Furthermore, it improves the physical and mental well-being of caregivers, who are spared the immediate, continuous burden of intensive pediatric diabetes management.[2]

Conclusions

A single 14-day course of teplizumab provides a statistically significant and clinically meaningful delay to the onset of clinical Stage 3 type 1 diabetes in non-diabetic individuals with Stage 2 disease.[8] Depending on the specific data cut and follow-up duration analyzed, the median delay ranges from 24.0 months to 32.5 months compared to placebo.[14] From a physiological perspective, this clinical delay is driven by the preservation and stabilization of endogenous beta-cell function (as demonstrated by C-peptide AUC and oral minimal model dynamics) and is mediated by the induction of a state of durable immunological tolerance.[15] This tolerance involves the functional exhaustion of pathogenic CD8+ effector memory T cells and the down-regulation of $IL7R$ signaling, preventing the expansion of autoantigen-reactive T-cell clones.[23]
While the short-term toxicities of teplizumab (such as transient lymphopenia, mild CRS, and

maculopapular rash) are clinically manageable with proactive escalational dosing and premedication protocols, the long-term clinical utility of this breakthrough therapy remains tied to a broader systemic challenge: the urgent clinical need to develop, standardize, and implement widespread, population-based autoantibody screening programs to identify pre-symptomatic Stage 2 individuals before clinical onset occurs.[2]

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