Early Diagnosis and Intervention for Type 1 Diabetes (T1D) – Progress from T1D TrialNet

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Today’s Agenda

1. Introduction
2. Who We Are & What We Do
3. The Path to Type 1 Diabetes
4. Intervention with TrialNet Research
5. Questions?
Type 1 Diabetes TrialNet

Who We Are & What We Do
We are an international network of leading academic institutions, physicians, scientists and healthcare teams at the forefront of type 1 diabetes research.
About Us

WHAT WE DO

Funded by the National Institutes of Health, we offer risk screening for relatives of people with type 1 diabetes and innovative clinical studies to preserve insulin production.
Using knowledge gained through clinical research, our mission is to prevent type 1 diabetes and stop disease progression by preserving insulin production before and after diagnosis.
T1D Disease Progression
The Path to Type 1 Diabetes
Genetic Risk

Immune Activation

Immune Response

Starting Point
If you have a relative: 15x greater risk of developing T1D

STAGE 1

STAGE 2

STAGE 3

STAGE 4

T1D Disease Progression
T1D Disease Progression

The Stages to Type 1 Diabetes

**STAGE 1**
- Normal Blood Sugar
- ≥ 2 autoantibodies
- **START OF T1D**

**STAGE 2**
- Abnormal Blood Sugar
- ≥ 2 autoantibodies

**STAGE 3**
- Clinical Diagnosis
- ≥ 2 autoantibodies

**STAGE 4**
- Long-standing T1D

Starting Point
If you have a relative: 15x greater risk of developing T1D

Genetic Risk

Immune Activation
Beta cells are attacked

Immune Activation
Development of single autoantibody
T1D Disease Progression

Starting Point
Genetic Risk

The path to T1D starts here

- Everyone who is diagnosed with T1D has the gene(s) associated with T1D
  - General population risk is 1 in 300
- Family members are at 15x greater risk to develop T1D
  - Relative risk is 1 in 20
T1D Disease Progression

Starting Point
If you have a relative: 15x greater risk of developing T1D

Genetic Risk

Immune Activation

Beta cells are attacked

STAGE 1

STAGE 2

STAGE 3

STAGE 4
Immune system is activated

**Immune Activation**

- Likely a common event
- Research taking place to identify the possible “event” or combination of “events”
T1D Disease Progression

Starting Point
If you have a relative: 15x greater risk of developing T1D

Genetic Risk

Immune Activation

Immune Response

STAGE 1

STAGE 2

STAGE 3

STAGE 4

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody
T1D Disease Progression

Development of single autoantibody

**Immune Response**

- Immune system responds to beta cells being attacked
- Results in the development of autoantibodies
- Autoantibodies are a “visible” signal that the immune system is activated
T1D Disease Progression

Progression by Population:

- Everyone who goes onto develop T1D has a genetic risk
- Immune system will be activated in some of those people
- Even fewer will go on to develop an autoantibody

Starting Point
- If you have a relative: 15x greater risk of developing T1D

Genetic Risk

Immune Activation
- Beta cells are attacked

Immune Response
- Development of single autoantibody

Stage 1

Stage 2
Genetic Risk

Immune Activation

Starting Point
If you have a relative: 15x greater risk of developing T1D

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

Immune Response

Type 1 Diabetes

Progression by Population:

- Essentially everyone with 2 or more autoantibodies will continue to progress towards clinical symptoms
- T1D starts when you develop two or more autoantibodies

T1D Disease Progression
Scientific Statement from JDRF, Endocrine Society, ADA

Staging Presymptomatic Type 1 Diabetes

In the October 2015 issue of Diabetes Care, the JDRF, American Diabetes Association (ADA), and Endocrine Society recommend adoption of a new type 1 diabetes staging classification.

The recommendation is largely based on an immense amount of data collected from TrialNet research spanning two decades and involving more than 150,000 relatives of people with type one diabetes.

Type one diabetes can now be most accurately understood as a disease that progresses in three distinct stages.
T1D Disease Progression

Genetic Risk

Immune Activation

Starting Point
If you have a relative: 15x greater risk of developing T1D

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

STAGE 1
Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

STAGE 2

STAGE 3

STAGE 4
Stage 1 T1D
Normal Blood Sugar

- START of T1D
- Two or more autoantibodies
- Normal blood sugar
- Lots of beta cells that are able to maintain blood sugar
- No symptoms
Genetic Risk

Starting Point
If you have a relative: 15x greater risk of developing T1D

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

STAGE 1
Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

STAGE 2
Abnormal Blood Sugar
≥ 2 autoantibodies

STAGE 3

STAGE 4

T1D Disease Progression
T1D Disease Progression

Stage 2 T1D
Abnormal Blood Sugar

≥ 2 autoantibodies

• Two or more autoantibodies
• Fewer beta cells, but not enough to keep blood sugar normal
• No symptoms
T1D Disease Progression

**Starting Point**
If you have a relative: 15x greater risk of developing T1D

**Genetic Risk**

**Immune Activation**

- Beta cells are attacked

**Immune Response**

- Development of single autoantibody

**STAGE 1**
- Normal Blood Sugar
- Abnormal Blood Sugar

**STAGE 2**
- Abnormal Blood Sugar

**STAGE 3**
- Clinical Diagnosis

**STAGE 4**

≥ 2 autoantibodies

START OF T1D

≥ 2 autoantibodies

≥ 2 autoantibodies
T1D Disease Progression

Stage 3 T1D
Clinical Diagnosis

- Marked by clinical diagnosis (Dx)
- Formerly known as “start of T1D”
- Even fewer beta cells
- Symptoms of high blood sugar

≥ 2 autoantibodies
T1D Disease Progression

Starting Point
If you have a relative: 15x greater risk of developing T1D

Genetic Risk

Immune Activation

Beta cells are attacked

Immune Response

Development of single autoantibody

STAGE 1

Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

STAGE 2

Abnormal Blood Sugar
≥ 2 autoantibodies

STAGE 3

Clinical Diagnosis
≥ 2 autoantibodies

STAGE 4

Long-standing T1D

The Stages to Type 1 Diabetes
T1D Disease Progression

Stage 4 T1D
Long-Standing T1D

- Continued loss of beta cells over time
- Research outside of TrialNet is working to replace or replenish beta cells
Genetic Risk

Immune Activation

Starting Point
If you have a relative: 15x greater risk of developing T1D

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

STAGE 1
Stage 1 is the back of the line (two or more autoantibodies, normal glucose tolerance)

STAGE 2
Stage 2 is the front of the line (two or more autoantibodies, abnormal glucose tolerance)

STAGE 3

STAGE 4

Children progress faster than adults
## T1D Disease Progression

The impact of AGE on disease progression & beta cell decline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age</th>
<th>STAGE 1 (Start of T1D)</th>
<th>STAGE 2</th>
<th>STAGE 3 (Clinical Dx)</th>
<th>STAGE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Start of T1D)</td>
<td>&lt;5</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-9</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>15-19</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 20</td>
<td>Long-standing T1D</td>
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</tbody>
</table>
1. **Type 1 diabetes** starts with two or more autoantibodies.

2. There are three defined stages:
   - **Stage 1:** Presence of 2 or more autoantibodies with normal blood sugar
   - **Stage 2:** Presence of 2 or more autoantibodies with abnormal blood sugar
   - **Stage 3:** Clinical diagnosis (Dx) of type 1 diabetes

3. Age matters!
   1. Time from 2 or more autoantibodies to Dx is faster the younger you are.
   2. Beta-cell decline is also faster the younger you are and continues through stage 4.
1. Accelerate the clinical development of therapies by providing a common framework for
   • Regulators, funders, academia and industry

2. Identification of T1D in its earliest stages can lead to a decreased risk of diagnosis in DKA

3. Staging diabetes allows us to treat T1D early to delay progression and ultimately prevent stage 3 (symptomatic T1D)
   • Treating high blood pressure, allows us to treat the disease early and ultimately prevent a heart attack or stroke
TrialNet Disease Intervention

Intervention with TrialNet Research
Using knowledge gained through clinical research, TrialNet’s mission is to prevent type 1 diabetes and stop disease progression by **preserving insulin production** before and after diagnosis.
• It starts with a program called **Pathway to Prevention**.

• Pathway to Prevention is a simple blood test to determine where you are on the path to T1D.
TrialNet Disease Intervention

P2P
Pathway to Prevention

Determine where you are on the path

• No cost
• 1st and 2nd degree relatives
• Screens for autoantibodies
• Based on results
  • Look to enroll in clinical trial to preserve beta cell function
  • Or monitor for disease progression
P2P
Pathway to Prevention

Eligibility Requirements

• Anyone between age 1 and 45 with a sibling, child or parent with type 1 diabetes
• Anyone between age 1 and 20 with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with T1D diabetes
• Those under 18 who do not have autoantibodies can be retested every year
TrialNet Disease Intervention

TN07
Oral Insulin

Stage 1 Prevention Study

• **START of T1D**
  • Two or more autoantibodies
    • Including Insulin Autoantibody (mIAA)
  • Normal blood sugar
  • Lots of beta cells that are able to maintain blood sugar
TrialNet Disease Intervention

TN07
Oral Insulin

Stage 1 Study Goal

- Delay conversion to abnormal blood sugar (Stage 2)
- Maintain current level of beta cell production
Study Rationale

- Effective in Diabetes Prevention Trial 1 (DPT1)
  - Showed delay in disease progression by up to 10 years in some participants
- Participants take a daily pill
  - Widely tolerated
TrialNet Disease Intervention

TN20
Immune Effects of Oral insulin

Stage 1 Mechanistic Study

• **START of T1D**
• Two or more autoantibodies
• Normal blood sugar
• Lots of beta cells that are able to maintain blood sugar
TrialNet Disease Intervention

TN20
Immune Effects of Oral Insulin

Stage 1 Mechanistic Study Goal

- Learn how different doses and intervals of oral insulin affect immune response
- Maintain current level of beta cell production
TrialNet Disease Intervention

TN20

Immune Effects of Oral Insulin

Mechanistic Study Rationale

- Complimentary study to TN07
- All study participants take Oral Insulin
  - Widely tolerated
TrialNet Disease Intervention

TN18
Abatacept (Orencia™)

Stage 1 Prevention Study

- **START of T1D**
- Two or more autoantibodies
- Normal blood sugar
- Lots of beta cells that are able to maintain blood sugar
TrialNet Disease Intervention

**TN18 Abatacept (Orencia™)**

**Stage 1 Study Goal**

- Delay conversion to abnormal blood sugar (stage 2)
- Maintain current level of beta cell production
**TrialNet Disease Intervention**

**TN18 Abatacept (Orencia™)**

### Study Rationale

- Approved & efficacious for treatment of:
  - Adult Rheumatoid Arthritis
  - Juvenile Idiopathic Arthritis
- Effective in TrialNet Abatacept New Onset Trial
  - Delayed beta cell decline by 9.5 months
1. These studies are for those identified in Stage 1 (the start of T1D)

2. Oral Insulin
   - Enrollment closed Dec 2015; Results expected—2017!

3. New Study! Immune Effects of Oral Insulin
   - Currently enrolling
   - Participate in Pathway to Prevention to identify eligibility

4. Abatacept
   - Currently enrolling
   - Participate in Pathway to Prevention to identify eligibility

TrialNet Disease Intervention Stage 1
TrialNet Disease Intervention

TN10
Teplizumab (Anti-CD3)

Stage 2 Prevention Study

- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
- No symptoms
TrialNet Disease Intervention

TN10
Teplizumab (Anti-CD3)

Study Goal

- Delay conversion to stage 3 (clinical diagnosis)
- Maintain current level of beta cell production
Study Rationale

• Anti-CD3 has been shown to improve the decline in insulin production in newly diagnosed (stage 3) patients in numerous clinical trials

• About half of individuals with T1D who participated in newly diagnosed (stage 3) anti-CD3 clinical trials required less insulin
1. This study is for those identified in Stage 2 (front of the line)

2. Teplizumab
   - Currently enrolling
   - Participate in Pathway to Prevention to identify eligibility
TrialNet Disease Intervention

TN19
ATG/GCSF

Treatment Study

- Marked by clinical diagnosis (Dx)
- Formerly known as “start of T1D”
- Even fewer beta cells
- Symptoms of high blood sugar
- Combination therapy—using two medications
TrialNet Disease Intervention

**TN19 ATG/GCSF**

**Study Goal**

- Maintain current level of beta cell production
TrialNet Disease Intervention

TN19
ATG/GCSF

Study Rationale

• Conducted pilot study that suggests benefit
• People who had type 1 diabetes for 4 months to 2 years continued making insulin for up to a year after treatment
1. This study is for those identified in Stage 3, clinical diagnosis
   • Formerly considered the start of T1D

2. ATG/GCSF
   • Currently enrolling
   • Must be enrolled in the trial within 100 days of clinical diagnosis
## TrialNet Disease Intervention at Every Stage

<table>
<thead>
<tr>
<th>P2P Pathway to Prevention</th>
<th>TN20 Immune Effects of Oral Insulin</th>
<th>TN18 Abatacept</th>
<th>TN10 Teplizumab (Anti-CD3)</th>
<th>TN19 ATG/GCSF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK SCREENING</strong></td>
<td><strong>STAGE 1</strong></td>
<td><strong>STAGE 1</strong></td>
<td><strong>STAGE 2</strong></td>
<td><strong>STAGE 3</strong></td>
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</table>

This study screens relatives of people with T1D to study risk and learn about how the disease occurs.

- Screens for five autoantibodies
- 1<sup>st</sup> and 2<sup>nd</sup> degree relatives
- First step to identify eligibility for clinical trial participation

Mechanistic study to learn how different doses and intervals of oral insulin affect immune response.

- 1<sup>st</sup> stage toward T1D
- 2 or more autoantibodies

This study test whether abatacept helps stop or slow beta-cell decline in people who are at high risk of developing T1D.

- 1<sup>st</sup> stage toward T1D
- 2 or more autoantibodies
- Approved and efficacious for treatment of RA/JIA

This study tests whether teplizumab helps stop or slow down beta-cell decline in people who are at high risk of developing T1D.

- 2<sup>nd</sup> stage toward T1D
- 2 or more autoantibodies with abnormal glucose tolerance

This study tests whether ATG used alone or together with GCSF will help people continue to produce their own insulin.

- 3<sup>rd</sup> stage diagnosis of T1D
- Combination therapy using two medications
Thank you!

Your Participation is Impactful

How to participate

• The TrialNet Northwest Clinical Center at Benaroya Research Institute
  • Nancy Wickstrom
  • diabetes@benaroyaresearch.org
  • 800-888-4187
• Or visit https://www.benaroyaresearch.org/ and enter “Pathway to Prevention” in search box.
Questions

Thank you!