Type 1 Diabetes

• Why does it occur?
• Is prevalence increasing?
• How is it treated?
• Will there be a cure?
• Synergy between genetic risk and environmental triggers
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
Starting Point
If you have a relative: 15x greater risk of developing T1D

Immune Activation
Beta cells are attacked

<table>
<thead>
<tr>
<th>STAGE 1</th>
<th>STAGE 2</th>
<th>STAGE 3</th>
<th>STAGE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Risk</td>
<td>Immune Activation</td>
<td>Immune Response</td>
<td></td>
</tr>
</tbody>
</table>
Immune system is activated

**Immune Activation**

- Likely a common event
- Research taking place to identify the possible “event” or combination of “events”
Development of single autoantibody

**Immune Response**

1 autoantibody

- 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
  - They do not cause the destruction of beta cells
Progression by Population:

- Everyone who goes on to 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
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
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

Immune Response

STAGE 1
Immune Activation
Beta cells are attacked

STAGE 2
Immune Response
Development of single autoantibody

Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

Abnormal Blood Sugar
≥ 2 autoantibodies
Stage 2 T1D
Abnormal Blood Sugar

≥ 2 autoantibodies

- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
  - Impaired glucose tolerance or “dysglycemia”
- No symptoms
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
Stage 4 T1D
Long-Standing T1D

Post diagnosis

- Continued loss of beta cells over time
- Research outside of TrialNet
  - Engineer’s approaches
    - Closed loop systems
  - Beta cell replacement
    - Whole pancreas transplant
    - Islets
    - Stem cell derived beta cells
<table>
<thead>
<tr>
<th>Age</th>
<th>STAGE 1 (Start of T1D)</th>
<th>STAGE 2</th>
<th>STAGE 3 (Clinical Dx)</th>
<th>STAGE 4 Long-standing T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - 9</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 - 14</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - 19</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥ 20</td>
<td></td>
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</tbody>
</table>

The impact of AGE on disease progression & beta cell decline
P2P  
Pathway to Prevention

Eligibility Requirements

• In immediate family:
  – Anyone between age 1 and 45 with a sibling, child or parent with type 1
• In extended family:
  – Anyone between age 1 and 20 with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with T1D
• Those under 18 who do not have autoantibodies can be retested every year

Tracy Rodriguez  
TrialNet Coordinator, UCSF
Increasing Incidence of T1DM

Projected increase in T1DM in USA from 1.25 to 5 million by 2050

- Finland
- Sweden
- Colorado
- Germany

Rewers M. Ann NYAS 2008
Diabetes in Youth

Rate of new cases of type 1 and type 2 diabetes among youth ages younger than 20 years, by race/ethnicity, 2002–2005

Rate (per 100,000 per year)

- Type 1
- Type 2

<10 years

10–19 years
**T1DM**

- Most common presentation in children and adolescents
- Approximately 50% new-onset < age 20
- Peak incidence
  - Puberty for boys and girls
- More common in Northern European heritage
- Autoimmune
- 1 of 350 children
- 3-5% risk in siblings
- 30% for identical twins
- Risk of DKA
- Dependence on insulin for survival
- Related autoimmune disorders
  - Thyroid - up to 15%
  - Celiac -5%

**T2DM**

- > 30% of children > 10 presenting with T2DM
- Insulin Resistance
- Obesity
- NAFLD
- PCOS
- Increasing prevalence
- [+ family history
- Ketosis can be present (KPT2)
- Life style mod, Metformin, insulin
- Elements of Metabolic Syndrome
  - HTN
  - Acanthosis Nigracans
  - Dyslipidemia
  - Microalbuminuria
DCCT: intensive control reduces complications in type 1 diabetes

Conventional versus intensive insulin therapy (n = 1441)

![Graph showing HbA1c levels over years of study for conventional and intensive treatment groups.]

Conventional treatment (n = 730)

Intensive treatment (n = 711)

\[ P < 0.001 \]

DCCT: intensive control reduces complications in type 1 diabetes

<table>
<thead>
<tr>
<th>A1C%</th>
<th>eAG mg/dL</th>
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<tbody>
<tr>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>5.5</td>
<td>111</td>
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<tr>
<td>6</td>
<td>126</td>
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<td>6.5</td>
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<tr>
<td>11</td>
<td>269</td>
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<tr>
<td>11.5</td>
<td>283</td>
</tr>
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<td>12</td>
<td>298</td>
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Average HbA1c By Age

*≤2 years old and ≥80 years old are pooled.
Treatment

• GOAL: Lowest A1c without significant hypoglycemia
• Monitor BG with SMBG or CGM
• Physiologic regimens whenever realistically possible including use of CSII pump therapy in all ages
• Use of CHO counting whenever possible
• Incorporating exercise/activity in plan
• Developmentally appropriate expectations
A1c goals for T1DM by age group

<table>
<thead>
<tr>
<th>Age</th>
<th>HbA1c</th>
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<tbody>
<tr>
<td>Youth</td>
<td>&lt; 7.5%</td>
</tr>
<tr>
<td>Adults</td>
<td>&lt; 6.5% (AACE)</td>
</tr>
<tr>
<td></td>
<td>&lt; 7.0% (ADA)</td>
</tr>
<tr>
<td>Elderly</td>
<td>individualized</td>
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</tbody>
</table>
Normal Physiology: Basal-Bolus Insulin

Optimize therapy?

A: pump  
B: infusion set  
C: sensor  
D: transmitter
Family Protective Factors in Chronic Illness

- Family emotional closeness or connectedness
- Caregiver (parental) coping skills
- Mutually supportive relationships
- Clear family organization & decision-making
- Direct communication about the illness

Family Risk Factors in Chronic Illness

- Conflict or criticism
- Psychological trauma related to the disease
- Stressors external to the family
- Family isolation
- Disruption of developmental tasks by the disease
- Family rigidity or perfectionism