General population screening for T1D: Experience from Sweden

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DiaUnion is a collaboration between Lund University and Steno Diabetes Center Copenhagen

DiaUnion started in 2020 with the aim to create a screening program in Sweden and Denmark for type 1 diabetes and related autoimmune diseases

DiaUnion’s first focus is to build an infrastructure for early detection of type 1 diabetes, celiac disease and autoimmune thyroid disease in the Öresund Region
Why the TRIAD?

- Type 1 Diabetes (T1D), Celiac Disease (CD), Autoimmune Thyroid Disease (AITD)
- Common chronic diseases affecting children and adolescents (0.5–3%)
- Frequently co-occurs in families
- No cure – lifelong treatment (insulin, gluten-free diet, levothyroxin)
- Clinical onset is preceded by the presence of disease-specific autoantibodies
Screening of children randomly invited from the general pediatric population in the Skåne County, Sweden

Screening of siblings (i.e., FDRs) of patients with T1D in Copenhagen, Denmark

FDR, first degree relatives.
Communication provided by speaker. The DiaUnion TRIAD study is a collaboration between Lund University, Steno Diabetes Center Copenhagen and Medicon Valley Alliance, for early detection of T1D and two genetically related autoimmune diseases (CD and AITD). For more information on the DiaUnion TRIAD study, including the predicted end date, see: https://portal.research.lu.se/en/projects/screening-for-Type-1-diabetes-celiac-disease-and-thyroiditis-in-c [Last accessed October 2023]
Feasibility of home sampling

• 3,527 consents (18.0%)
• 4,123 kits sent out
• 2,315 blood samples of sufficient volume (65.6%)
• 1,112 no sample (31.5%)
• 91 active withdrawals
  • 58 due to concerns about blood draw (63.7%)

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Screening of Swedish children

Skåne County, Sweden (n=1.4 million)
- Two age groups:
  - 6–9 years
  - 13–16 years
- General population (n=68,000)
- Invitation to screening (n=20,000)

Home capillary sampling kit
- Kit sent to home address
- Finger prick (>250 uL)
- Samples sent back to the lab by regular mail

Detection of eight autoantibodies:
- T1D (IAA, GADA, IA-2A, ZnT8A)
- CD (IgA-tTG, IgG-tTG)
- AITD (TPOA, THGA)
  - 1. Radiobinding assays (RBA); chemiluminescent immunoassay
  - 2. Antibody-detection by agglutination-PCR (ADAP)

(Aab+) children:
- A second sample median 3.8 (range 1.9–15) mo
- Persistent Aab+ children referred to pediatrician for clinical follow-up

ADAP, agglutination-PCR; GADA, glutamic acid decarboxylase antibodies; IAA, insulin autoantibodies; IA-2A, IA-2 autoantigen; IgA, immunoglobulin A; IgG, immunoglobulin G; THGA, thyroglobulin autoantibodies; TPOA, thyroperoxidase autoantibodies; tTG, tissue transglutaminase; ZnT8A, zinc transporter 8 autoantibody. Communication provided by speaker. The DiaUnion TRIAD study is a collaboration between Lund University, Steno Diabetes Center Copenhagen and Medicon Valley Alliance, for early detection of T1D and two genetically related autoimmune diseases (CD and AITD). For more information on the DiaUnion TRIAD study, including the predicted end date, see: https://portal.research.lu.se/en/projects/screening-for-Type-1-diabetes-ceeliac-disease-and-thyroiditis-in-c (last accessed October 2023)
Quality of samples

Days between sample draw date and sample process date (registered in 2,236 samples)

HEMOLYSIS?
(registered in 2,301 samples)

- No hemolysis: n=1,471 (63.6%)
- Moderate hemolysis: n=620 (26.9%)
- Gross hemolysis: n=210 (9.1%)

Median: 2 days

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Results of screening (n=2271)

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T1D n=3 (5% of T1D Aab+, 0.1% of screened)
CD n=26 (42.6% of CD Aab+, 1.1% of screened)
AITD n=6 (6% of AITD Aab+, 0.3% of screened)

T1D Aab+ n=60 (2.6% of screened)
CD Aab+ n=61, (2.7% of screened)
AITD Aab+ n=99, (4.4% of screened)
Aab+ for multiple TRIAD diseases n=9 (0.4% of screened)

Diagnosed after screening n=35 (1.5%)
Positive autoantibodies
"At risk individuals" n=176
Recruited to clinical intervention study (PAL) n=65
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Clinical follow-up

**Screening sample islet Aab+**

- **Aab− + Normal HbA1c**
  - Information from pediatrician
  - No follow-up

- **Aab+ + Normal HbA1c**
  - Information from pediatrician about risk
  - Information about intervention study, if eligible

- **Aab+ + Abnormal HbA1c**
  - Information from pediatrician

**Confirmatory sample + HbA1c**

- **Multiple Aab+ HbA1c every 3 months for 1 year**
  - Information from pediatrician

- **Single Aab+ HbA1c after 1 year**
  - Information from pediatrician

**Aab+**

- Referral to pediatric clinic; OGTT

OGTT, oral glucose tolerance test. Communication provided by speaker. The DiaUnion TRIAD study is a collaboration between Lund University, Steno Diabetes Center Copenhagen and Medicon Valley Alliance, for early detection of T1D and two genetically related autoimmune diseases (CD and AITD). For more information on the DiaUnion TRIAD study, including the predicted end date, see: https://portal.research.lu.se/en/projects/screening-for-Type-1-diabetes-celiac-disease-and-thyroiditis-in-c [Last accessed October 2023]
TRIAD among family members

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TRIAD among family members

30% of Aab+ children had an FDR with a TRIAD-disease

>2/3 were mothers
AITD was the most common disease in mothers (70%)

>1/6 were fathers
T1D was the most common disease in fathers (50%)

<1/6 were siblings
CD was the most common disease in siblings (63%)

In 52% the FDR had another disease than the child was screened positive for
Screening of Danish T1D FDRs

1. Biobank samples (no follow up; n=1,420)
2. ADAP used as the screening assay
3. RBA used to confirm Aab+

**Aab+ results confirmed by RBA showed:**

Any TRIAD autoantibody:
- 13.5% Danish T1D FDRs
- 5.6% of Swedish pediatric GP

Any T1D autoantibody:
- 7.5% of Danish T1D FDRs
- 1.1% of Swedish pediatric GP

Multiple T1D autoantibodies:
- 4.6% of Danish T1D FDR
- 0.6% of Swedish pediatric GP

<table>
<thead>
<tr>
<th>Aab+</th>
<th>Danish T1D FDRs N=192/1,420 (13.5%)</th>
<th>n/N (%)</th>
<th>Swedish children N=127/2,271 (5.6%)</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GADA</td>
<td>89/1,420 (6.3%)</td>
<td>22/2,272 (1.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAA</td>
<td>43/1,420 (3.0%)</td>
<td>8/2,272 (0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA-2A</td>
<td>38/1,420 (2.7%)</td>
<td>8/2,272 (0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZnT8</td>
<td>28/1,420 (2.0%)</td>
<td>3/2,271 (0.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPOA</td>
<td>55/1,420 (3.9%)</td>
<td>52/2,272 (2.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tTGA</td>
<td>55/1,420 (3.9%)</td>
<td>55/2,272 (2.4%)</td>
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</tbody>
</table>

GP, general population. Communication provided by speaker. The DiaUnion TRIAD study is a collaboration between Lund University, Steno Diabetes Center Copenhagen and Medicon Valley Alliance, for early detection of T1D and two genetically related autoimmune diseases (CD and AITD). For more information on the DiaUnion TRIAD study, including the predicted end date, see: https://portal.research.lu.se/en/projects/screening-for-Type-1-diabetes-celiac-disease-and-thyroiditis-in-c [Last accessed October 2023]
Results of 2nd screening

DiaUnion 1.5 (2022–2023):

1. Swedish general pediatric population:
   - 1. ADAP screening assay
   - 2. RBA confirmation assay
   - 13,498 children ages 6–9 years and 13–16 years invited
   - So far 2407 children enrolled, 17.8% consent rate (Fig.1)
   - So far 1553 samples collected, 11.5% participating rate (Fig.2)
   - 31 (2.0%) reported a TRIAD disease (1.0% CD, 0.2% T1D, 0.1% AITD)
   - 333 (21.4%) children reported to have a FDRs with TRIAD disease

2. Danish T1D-FDRs (siblings, children, parents):
   - Age <40 years, 1,500 invited to screening
   - ADAP screening assay
   - RBA confirmation assay
   - Analysis pending

Fig. 1. Consent rate
Fig. 2. Sample rate
**ADAP vs RBA for GADA**

**DiaUnion 1.0 (2021-2022)**
- 2273 samples analysed in both ADAP and RBA
- The concordance agreement, Cohen’s kappa $\kappa$ coefficient, between the assays were 0.542
- Prevalence of confirmed GADA 1.0%

**DiaUnion 1.5 (2023)**
- ADAP first-line screening (cut-off 98th percentile)
- RBA confirmation assay
- 44/957 (4.6%) above cut-off in ADAP
- 13/44 (29.5%) confirmed GADA positive in RBA
- Prevalence of confirmed GADA 1.4%
ADAP vs RBA for tTGA

**DiaUnion 1.0 (2021-2022)**
- 2273 samples analysed in both ADAP & RBA
- The concordance agreement, Cohen’s kappa κ coefficient, between the assays were 0.698 (IgA) and 0.675 (IgG)
- Prevalence of confirmed tTGA 2.4%

**DiaUnion 1.5 (2023)**
- ADAP first-line screening (cut-off 75th percentile)
- RBA confirmation assay
- 222/957 (23.2%) above cut-off in ADAP
- 33/222 (14.9%) confirmed tTGA (IgA+IgG) positive in RBA
- Prevalence of confirmed tTGA 3.4%
**ADAP vs RBA for TPOA**

### DiaUnion 1.0 (2021-2022)
- 2273 samples analysed in both ADAP & RBA
- The concordance agreement, Cohen’s kappa $\kappa$ coefficient, between the assays were 0.595
- Prevalence of confirmed TPOA 2.3%

### DiaUnion 1.5 (2023)
- ADAP first-line screening (cutoff 90th percentile)
- RBA confirmation assay
- 44/957 (4.6%) above cut-off in ADAP
- 27/44 (61.4%) confirmed positive in RBA
- Prevalence of confirmed TPOA 2.8%
• DiaUnion boosts screening for T1D by including CD and AITD
• DiaUnion’s 1st screening of the Swedish GP population found islet autoimmunity in 2.6%, multiple islet autoantibodies in 0.6%, and T1D in 0.1%
• Results DiaUnion’s 2nd screening of the Swedish GP population pending, but confirms consent rate (18%) and successful participation rate (12%).
• Home sampling is feasible, but can be optimized by collecting smaller sample volumes for multiplex assays
• The multiplex ADAP assay is promising as a screening method, but further evaluation is needed before considering it as first-line screening for the GP
• DiaUnion’s next goal is to scale up screening to 30,000 Swedish children from the GP and 15,000 Danish T1D FDRs
Thank you!

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