Monitoring of Adults with Pre-symptomatic T1D

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Goals of Monitoring in Early T1D: Pediatric and Adult

- Prevent DKA and hospital admission
- Identification for therapy to delay Stage 3 T1D, prolong β-cell function
- Determine when to start insulin
- Minimize HbA1c
- Referral for participation in research studies

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Monitoring in Adults

Why different in adults?
1) Less studied

Many gaps in evidence base – most data on monitoring protocols from pediatric population

Box 1. Established population-based screening and monitoring studies in early-stage T1D*

ASK	Autoimmunity Screening for Kids program(7)
BABYDIAB	Part of the international Type 1 Data Intelligence (T1DI) project(15)
DAISY	Diabetes Autoimmunity Study in the Young(6)
DIPP	Type 1 Diabetes Prediction and Prevention Study based in Finland(11)
DPT-1	Diabetes Prevention Trial–Type 1(12)
ENDIT	European Nicotinamide Diabetes Intervention Trial(13)
Fr1da	Population-based healthcare research study based in Bavaria, Germany(9)
INNODIA	Global partnership between academic institutions, commercial partners and patient organizations(14)
SEARCH	SEARCH for Diabetes in Youth study(8)
TEDDY	The Environmental Determinants of Diabetes in the Young Study(5)
TrialNet	US-based research network centred on delaying or preventing T1D(10)

* Note, these are major research networks but this is not an exhaustive list.

No published guidance for IAb+ Adults

ISPAD GUIDELINES

ISPAD WILEY

ISPAD clinical practice consensus guidelines 2022: Stages of type 1 diabetes in children and adolescents

Rachel E. J. Besser[1] | Kirstine J. Bell[2] | Jenny J. Couper[3,4] | Anette-G. Ziegler[5] | Diane K. Wherrett[6] | Mikael Knip[7] | Cate Speake[8] | Kristina Casteels[9,10] | Kimberly A. Driscoll[11] | Laura Jacobsen[12] | Maria E. Craig[13] | Michael J. Haller[12]

Monitoring in Adults

Why different in adults?

2) Misdiagnosis!

- Misdiagnosis of T1D in adults is common, increases with age
- Can lead to **DKA** due to prescribing wrong therapy
- Lack of awareness among primary care providers

T1D confused for:

- Type 2 DM
- Ketosis prone T2D
- MODY
- Type 3C DM
- Pancreatic cancer
- Checkpoint inhibitor associated DM

40% of those developing T1D after age 30 are initially treated as T2D

No single clinical feature confirms T1D

- Age
- BMI
- DKA

-Gregory GA et al. International Diabetes Federation Diabetes Atlas Type 1 Diabetes in Adults. Lancet Diabetes Endocrinol 2022.
-Holt RIG et al. The management of type 1 diabetes in adults. A consensus report by the ADA and EASD. Diabetologia, 2021.

Monitoring in Adults

Why different in adults?

3) Slower progression

- Adults may not present with the classic symptoms of T1D and may not require insulin for months after diagnosis.
- Rate of progression in IAb+ adults < children.
- Many adults with multiple IAb+ still develop stage 3 disease
  - Some may never progress to stage 3
  - Some who do progress have a single IAb+
- Adults often with higher C-peptide at clinical diagnosis and slower decline of β-cell function over time.

-Lawrence JM et al. Incidence and predictors of type 1 diabetes among younger adults aged 20-45 years: the diabetes in young adults (Diya) study. Diabetes Research and Clinical Practice 2021.

T1D is diagnosed more commonly in adulthood vs. childhood

Annals of Internal Medicine

OBSERVATION: BRIEF RESEARCH REPORT

Age at Diagnosis in U.S. Adults With Type 1 Diabetes

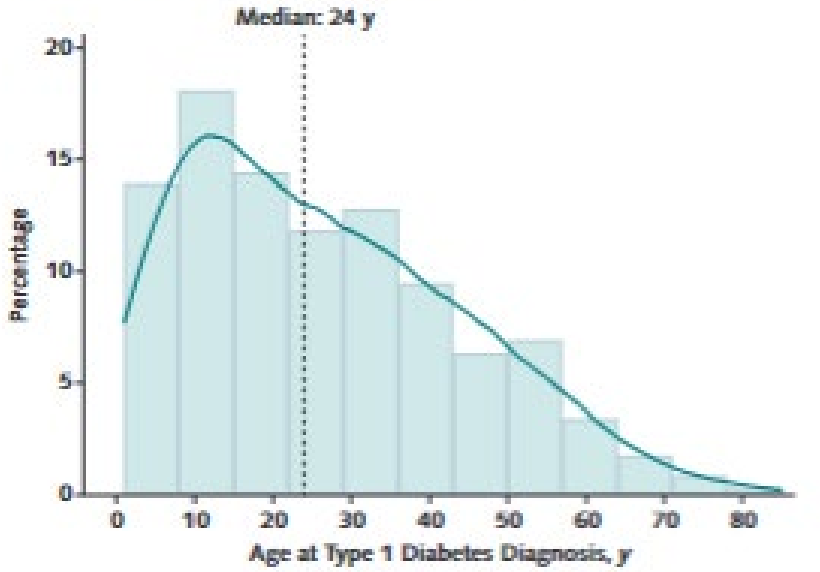
Background: Adult-onset type 1 diabetes is frequently misdiagnosed as type 2 diabetes, leading to inappropriate care (1). Emerging data suggest that up to 62% of type 1 diabetes cases develop after age 20 years (2). However, prior studies have been done in selected clinical populations. Clarifying the burden of adult-onset type 1 diabetes in the general population may help reduce misdiagnosis.

Objective: To characterize the age distribution of type 1 diabetes diagnosis in the United States, overall and according to demographic and clinical characteristics.

Methods: The National Health Interview Survey (NHIS) is a

- 37% with diagnosis of T1D **after age 30**
- Higher for men
- Higher for racial/ethnic minority adults

Figure. Distribution of age at diagnosis in U.S. adults with type 1 diabetes ($n = 947$), NHIS, 2016 to 2022.



The histogram and kernel density plot were based on the NHIS 2016, 2017, 2019, 2020, 2021, and 2022 cycles. Data on diabetes type were unavailable in 2018. NHIS = National Health Interview Survey.

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Monitoring in Adults

Why different in adults?

3) Slower progression

Defining Pathways for Development of Disease-Modifying Therapies in Children With Type 1 Diabetes: A Consensus Report

*Diane K. Wherrett,[1] Jane L. Chiang,[2] Alan M. Delamater,[3] Linda A. DiMeglio,[4] Stephen E. Gitelman,[5] Peter A. Gottlieb,[6] Kevan C. Herold,[7] Daniel J. Lovell,[8] Trevor J. Orchard,[9] Christopher M. Ryan,[10] Desmond A. Schatz,[11] David S. Wendler,[12] Carla J. Greenbaum,[13] and the Type 1 Diabetes TrialNet Study Group**

Diabetes Care 2015;38:1975–1985 | DOI: 10.2337/dc15-1429

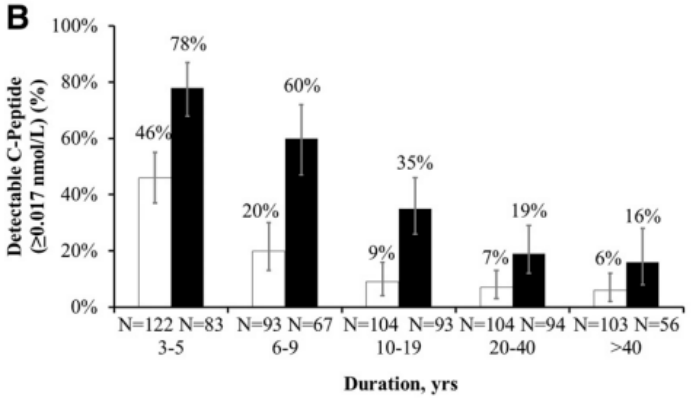

Figure 3—Impact of age on C-peptide after diagnosis. *A*: Model-based estimates of average slopes of C-peptide area under the curve (AUC) over time according to age quartiles (age-groups 7.7–12.3 years, 12.4–14.7 years, 14.8–21.2 years, and 21.4–46.1 years). Data from 191 TrialNet clinical trial participants. Reprinted with permission from Greenbaum et al. (63). *B*: Proportion of participants with detectable (≥0.017 nmol/L) nonfasting C-peptide according to age at diagnosis and duration of type 1 diabetes. White bars, those diagnosed at age ≤18 years; black bars, those diagnosed at age >18 years. Data from the T1D Exchange residual insulin study. Reprinted with permission from Davis et al. (64).

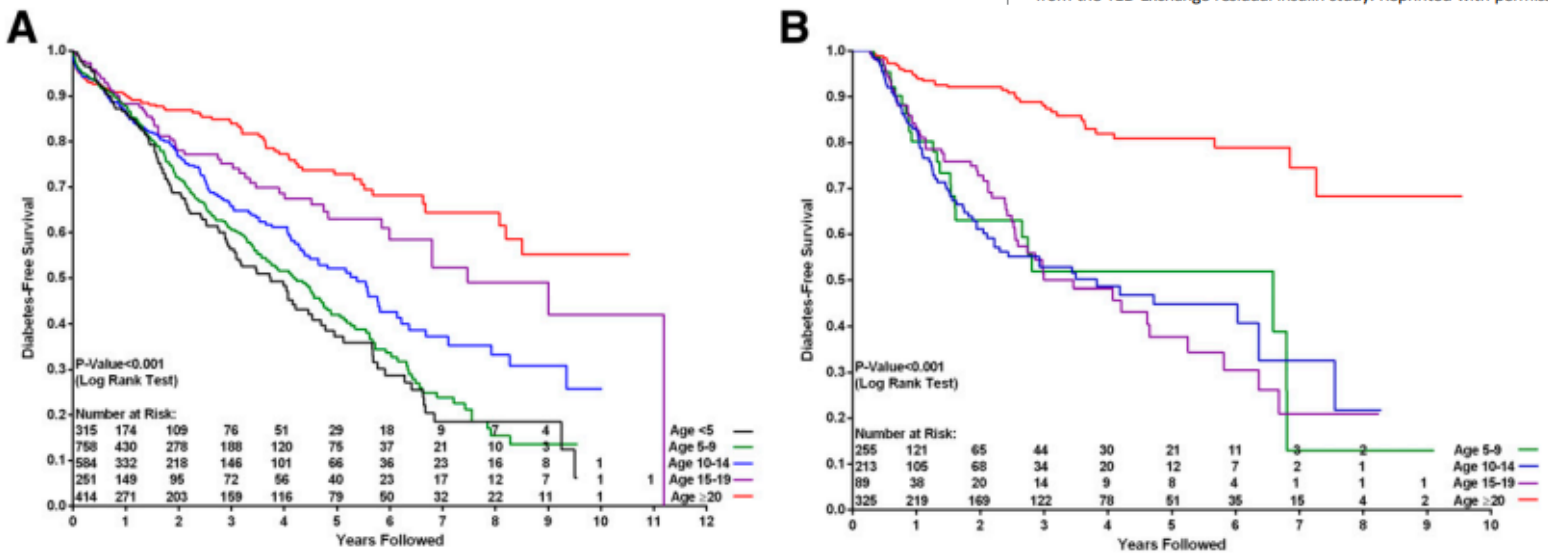

Figure 2—Impact of age on risk for disease progression in antibody-positive relatives participating in TrialNet Pathway to Prevention Study. *A*: Life table of progression to diabetes according to age in double antibody–positive relatives. *B*: Life table of progression to diabetes according to age in double antibody–positive subjects from time of abnormal glucose tolerance.

Monitoring in Adults

Why different in adults?

4) The challenge of LADA

Latent Autoimmune Diabetes in Adults (LADA)

- Slow auto-immune β-cell destruction leading to a long duration of marginal insulin secretion.
- Debate whether entity should be called LADA or T1D
  - No universal agreement on classification, diagnosis and management.
- Often misclassified as T2D
- Insulin should be initiated prior to clinical deterioration/ DKA.
  - Low or undetectable C-peptide

T2D - like phenotype
-C-peptide present
-intermediate for adiposity, insulin secretion

T1D phenotype
-C-peptide Absent

-Often single IAb+
-GADA most common
-Ab can disappear after 10 years

-Elsayed NA et al. Classification and diagnosis of diabetes: standards of care in diabetes – 2023. Diabetes Care 2023.
-Holt RIG et al. The management of type 1 diabetes in adults. A consensus report by the ADA and EASD. Diabetologia, 2021.
-Hernandez M et al. Latent Autoimmune Diabetes in Adults: A review of clinically relevant issues. Adv Exp Med Biol 2020.
-Yin W et al. Latent autoimmune diabetes in adults: a focus on beta-cell protection and therapy. Frontiers in Endocrinol 2022.

Consensus guidance for monitoring persons with islet autoantibody-positive pre-Stage 3 type 1 diabetes

Moshe Phillip[1,2], Peter Achenbach[3,4], Ananta Addala[5,6], Anastasia Albanese-O'Neill[7], Tadej Battelino[8,9], Kirstine J Bell[10], Rachel E J Besser[11,12], Ezio Bonifacio[3,13,14], William T Cefalu[15], Helen M Colhoun[16,17], Jennifer Couper[18,19,20], Maria Craig[10,21], Thomas Danne[22], Carine de Beaufort[23, 24, 25], Klemen Dovc[8,9], Kimberly A Driscoll[26,27], Sanjoy Dutta[28], Osagie Ebekozien[29], Helena Elding Larsson[30,31], Daniel J Feiten[32], Brigitte Frohnert[26], Robert A Gabbay[33], Mary Pat Gallagher[34], Carla J Greenbaum[35], Kurt J Griffin[36], William Hagopian[37], Michael J Haller[38, 39], Christel Hendrieckx[40,41,42], Emile Hendriks[43], Richard I G Holt[44,45], Lucille Hughes[46], Heba M Ismail[47], Laura Jacobsen[38], Suzanne B Johnson[48], Leslie E Kolb[49], Anne Koralova[50], Olga Kordonouri[22], Karin Lange[51], Robert W Lash[52], Åke Lernmark[30], Ingrid Libman[53], Markus Lundgren[30], David M Maahs[5], M Loredana Marcovecchio[54], Chantal Mathieu[55], Kellee Miller[29], Holly K O'Donnell[26], Tal Oron[1,2], Shivajirao P Patil[56], Rodica Pop-Busui[57], Marian J Rewers[26], Stephen S Rich[58], Desmond A Schatz[59], Rifka Schulman-Rosenbaum[60], Kimberly Simmons[26], Emily K Sims[61], Jay S Skyler[62], Laura Smith[63], Cate Speake[35], Andrea K Steck[26], Nick Thomas[64], Ksenia N Tonyushkina[65], Ritta Veijola[66], John Wentworth[67,68], Diane Wherrett[69], Jamie Wood[70], Anette Ziegler[3], Linda A DiMeglio[47]

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Monitoring in Adults

Why different in adults?

5) Pregnancy

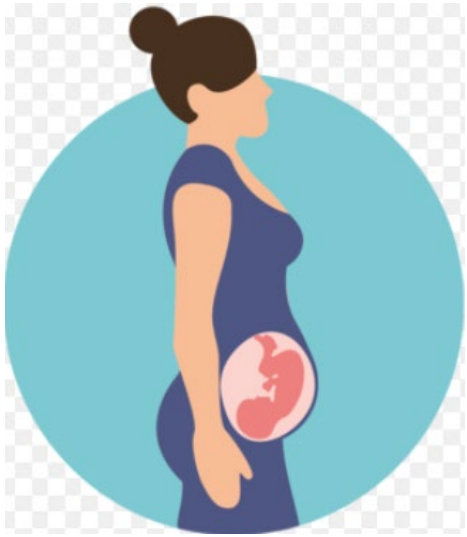


Table 3. Attributes of current monitoring methods

Method	Pros	Cons	Metrics obtained
Standard OGTT	• Gold standard • Used to stage disease and predict progression	• Requires glucose load and 2-5x blood draws over 2 hrs	• Glycemic staging • Risk scores for progression (DPTRS, DPTRS60, Index60, M60, M120)(80,144–148)
Abbreviated OGTT	• Similar to test for GDM, performed routinely in primary care	• Requires 2x blood draws, fasting and at 2 hrs	• 120 min OGTT-derived glucose • M120
Random venous glucose	• One-off sample • Low cost	• Requires a blood draw • Less sensitive than 120-min OGTT	• Similar to 120 min OGTT-derived glucose(82) • Postprandial is more sensitive.
HbA1c	• Highly specific • Can use capillary sample • Longitudinal HbA1c may be as precise as OGTT(62)	• Indicates 3-month average. Often normal in asymptomatic or recent-onset Stage 3 T1D • May be affected by age, non-diabetic disease states (e.g., renal, hematological syndromes)	• Risk of progression to "clinical disease": HbA1c >5.7%(149) • 10% rise from baseline (at first IAb$^+$) over 3-12 months (62,63), indicates dysglycemia and progression to Stage 2. • Consider use of CGM if 10% rise in HbA1c is confirmed, or higher-frequency of SMBG, to monitor risk for progression
CGM	• Can be used at home • Can be blinded for physician review only in some regions • Optimal duration of CGM wear is validated in adults and children >2 yrs with T1D, at all glycemic levels(150)	• Risk of anxiety for unblinded user seeing CGM fluctuations • Requires appropriate education on use and interpretation • Many primary care HCPs are unfamiliar with interpretation • Cost and access issues	• Sensitive in detecting individuals with asymptomatic Stage 3 T1D and dysglycemia in Stage 2 T1D(66) • Risk of progression to 'clinical disease': 10% > 7.8 mmol/L (>140 mg/dL)(65) • ≥5% time with glucose ≥140 mg/dL is predictive of progression to stage 3 T1D(64) • Other positive predictive value (PPV) metrics not tested.
SMBG	• Simple to use at home • Comparatively low cost	• Uncomfortable for users, can affect accuracy and adherence • Optimal timing and frequency have not been determined.	• Immediate capillary blood glucose test result
C-Peptide	• Measure of β-cell function. • Wide range of values at clinical diagnosis and persistent, but low levels of secretion can be seen long after diagnosis.	• Can be falsely low in hypoglycemia or severe hyperglycemia/DKA, so concomitant serum glucose should be checked for interpretation. • Presence of C-peptide does not exclude T1D and on its own is not useful for staging or diagnosis of T1D	• <0.2 nmol/L with IAb$^+$ status confirms diagnosis in Stage 3 T1D, distinct from other forms of diabetes with low pancreatic function but without autoimmune etiology. • Postprandial C-peptide
Repeat antibody testing	• Confirms initial IAb$^+$ test result and progression to multiple IAb$^+$ status	• None	• Autoantibody type and single IAb$^+$ or multiple IAb$^+$ status

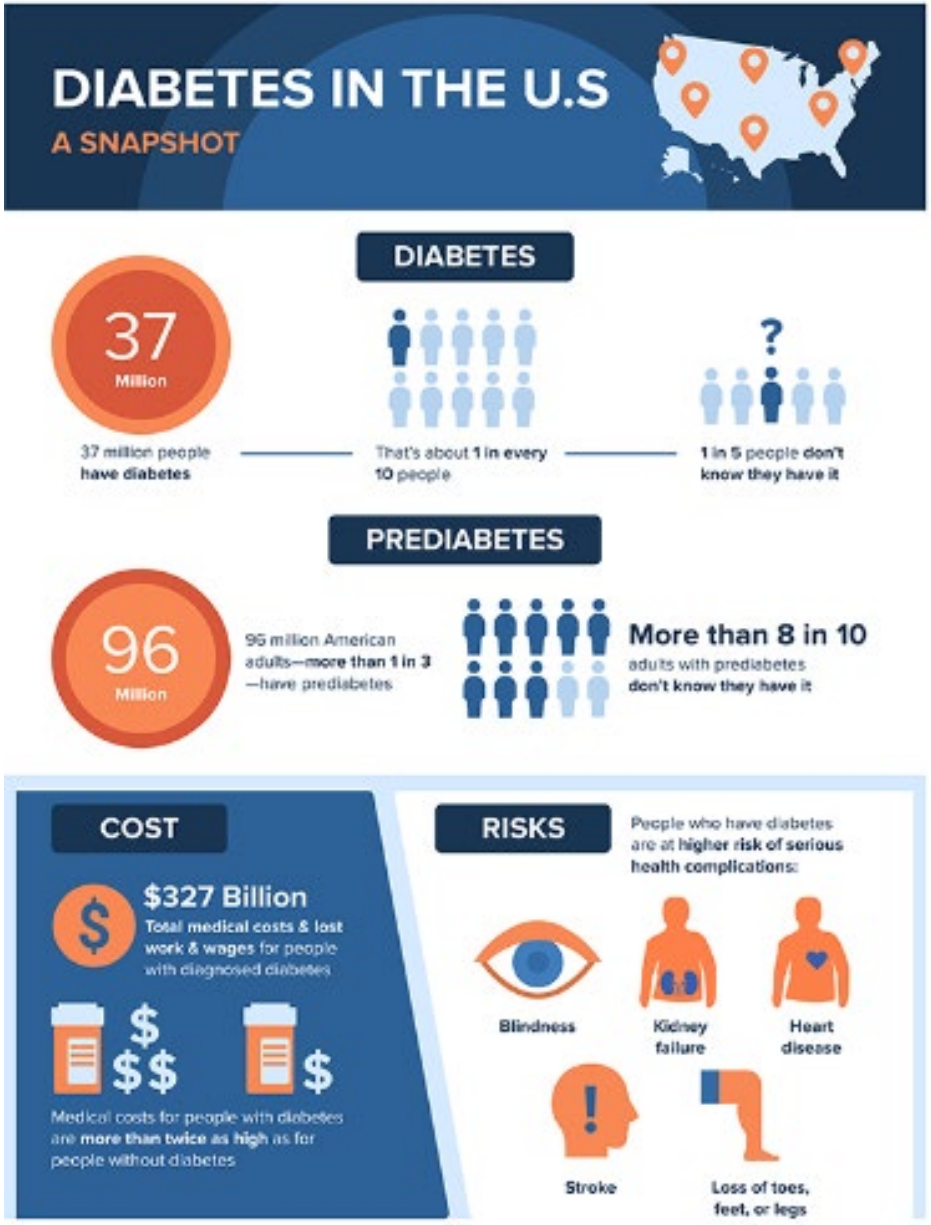
Single IAb+ Adults

Monitoring in single IAb⁺ adults

- Confirm persistent single IAb⁺ status after first detection in a second sample, preferably in a reference laboratory using a different assay format. **[A]**
- Although single IAb⁺ adults are at lower risk of progression to T1D compared to children (52), and this risk continues to fall with increasing age, there remains a residual risk for progression. The monitoring approach for single IAb⁺ adults can be informed by that applied for screening for T2D, which is recommended for adults aged >35 years, or who are overweight/obese with one or more of the following risk factors (18): **[A]**
  - High-risk race/ethnicity
  - History of CVD
  - Hypertension
  - Hypercholesterolemia

  Screening every 3 years for T2D in this context is sufficient for adults with normal blood glucose levels (97–99). This frequency of monitoring of adults with confirmed single IAb⁺ status is also probably sufficient because their risk of T1D progression is relatively low. **[E]**
- Annual monitoring should be considered for single IAb⁺ if there are additional risk factors, including one or more of: first-degree relative with T1D; dysglycemia (e.g. impaired fasting glucose or impaired glucose tolerance) or; history of stress hyperglycemia (100,101). **[E]**
- No T1D monitoring is indicated in transient, single IAb⁺ individuals who then revert to seronegative. Screening for diabetes should follow standard of care guidelines for T2D **[E]**

The Diabetes Epidemic (Type 2)



- **T2DM** screening – current recommendations
  - **United States Preventive Services Task Force** – adults age 35-70 with overweight or obesity
  - **American Diabetes Association** - adults age 35+ or with overweight, obesity +other risk factor

- US Preventative Services Task Force; Karina W Davidson, Michael J Barry, Carol M Mangione et al. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. JAMA. 2021; 326(8):736-743.
- American Diabetes Association. Standards of Medical Care in Diabetes – 2023 Classification and Diagnosis of Diabetes. Diabetes Care. 2023;46: S19-S40.

https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html
https://diabetes.org/about-us/statistics

Multiple IAb+ Adults

Monitoring for multiple IAb⁺ adults

- Confirm persistent multiple IAb⁺ status after first detection in a second sample, preferably in a reference laboratory, following the 'rule of twos' (46). **[A]**
- In infrequent cases when adults previously with confirmed multiple IAb⁺ status have reverted to single or negative IAb⁺ status (81), monitoring should also follow the guidelines below. **[C]**
- All multiple IAb⁺ adults should receive SMBG meters and strips, to be used during illness or when symptoms may be present. **[E]**
- In adults with Stage 1 T1D and normoglycemia (Table 1): HbA1c should be monitored every 12 months as part of routine primary care visits. **[E]**
- If duration of normoglycemia extends to 5 years, monitoring HbA1c every 2 years is sufficient. **[E]**
- In adults with Stage 2 T1D (Table 1), HbA1c should be monitored every 6 months. **[E]**
- Longitudinal change in HbA1c of >10% from date of confirmed seroconversion indicates dysglycemia and disease progression (62,63), perform an OGTT to assess T1D stage (Table 1) in order to determine eligibility for therapy.
- If progression to Stage 2 T1D is confirmed, consider use of blinded CGM every 6 months or higher-frequency of SMBG testing every 6 months (bi-weekly testing, in fasting or 2-hour postprandial state). **[E]**

Multiple IAb+ Adults

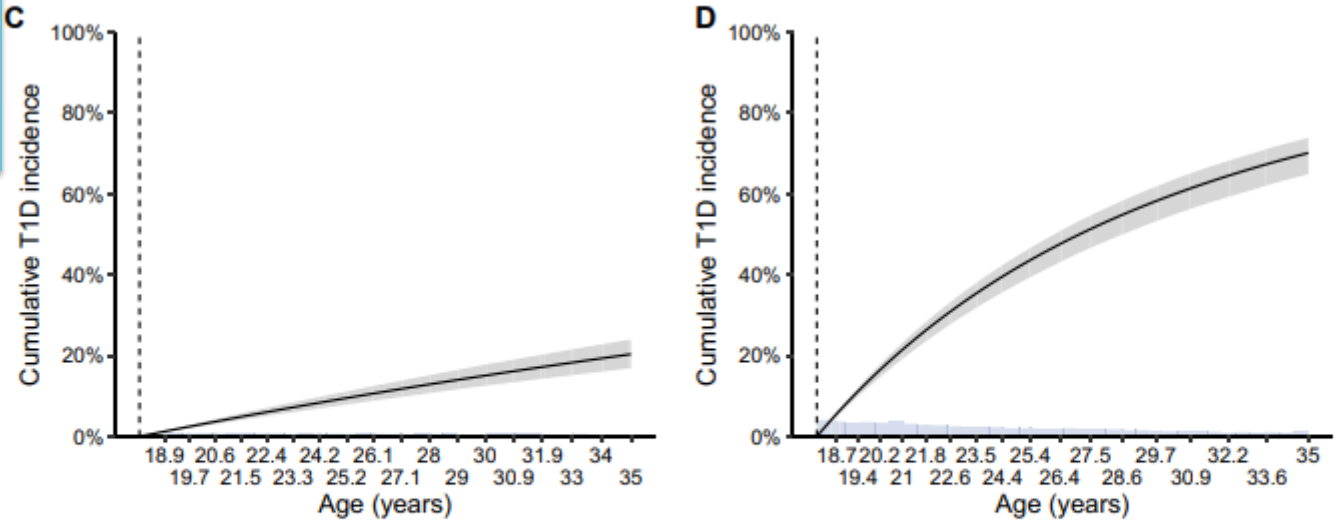
- Risk factors for T2D should be reviewed in all multiple IAb$^+$ adults, using appropriate metrics (central adiposity, BMI, hyperlipidemia, etc.) and as part of standard surveillance for T2D. **[B]** Modifiable risk factors like central obesity should be treated according to standards of care for T2D (18). **[A]**
- C-peptide monitoring should be considered where the diagnosis of T1D vs T2D is unclear (≤0.20 nmol/L cut-off with IAb$^+$ status is diagnostic for T1D) (102) and for deciding whether to start insulin. **[A]**
- Adults already diagnosed with diabetes mellitus with clinical suspicion of T1D (hyperglycemia, low C-peptide, non-obese body habitus) and ≥1 IAb$^+$ should be diagnosed with T1D and initiated on insulin. **[C]** Education should be provided on recognizing ketosis and individuals started on CGM if possible. **[B]**
- Adults with previously diagnosed Stage 3 T1D (Table 1), and in the 'honeymoon period', not being treated with insulin, should be monitored (Table 3) and provided with education on ketosis to ensure a low risk of developing DKA. In the absence of CGM, monitoring with SMBG should be performed daily. **[E]**

The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, 688–696
https://doi.org/10.1210/clinem/dgac594
Advance access publication 13 October 2022
Clinical Research Article

Risk Modeling to Reduce Monitoring of an Autoantibody-Positive Population to Prevent DKA at Type 1 Diabetes Diagnosis

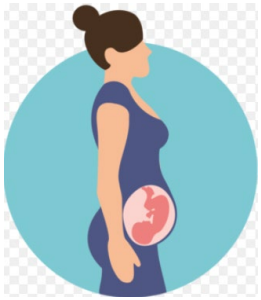
Colin O'Rourke,[1] Alyssa Ylescupidez,[1] Henry T. Bahnson,[1] Christine Bender,[1] Cate Speake,[1] Sandra Lord,[1] and Carla J. Greenbaum[1]

Adult single IA+:
18 visits over 17 years



Adult multiple IA+:
17 visits over 17 years

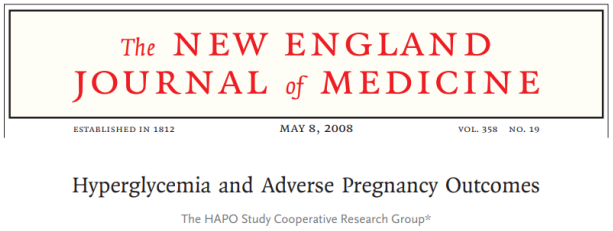
Figure 4. Cumulative incidence of type 1 diabetes (T1D) with monitoring schedule optimized to achieve approximately an average of 6 months undiagnosed time within each cohort. Cumulative incidence of T1D (with 95% confidence intervals) with optimized visit schedule for monitoring between ages 1 and 18 years for single and multiple autoantibody-positive (AABs) (pediatric cohort A, B) and for monitoring between ages 18 and 35 (adult cohort C, D). The optimized visit schedule is determined by setting the expected undiagnosed time as not greater than 6 months. Tick marks along the x-axis have been placed at these chosen visits. The vertical shaded bars along the x-axis represent the incidence within the visit window. A nominal 6 months of average undiagnosed time is achieved with A, 17 visits for the pediatric single AAB+ population; B, 14 visits for the pediatric multiple AAB+ population; C, 18 visits for the adult single AAB+ population; and D, 17 visits for the adult multiple AAB+ population.



IAb+ Adults and Pregnancy

- High risk time for mother and fetus
- Hyperglycemia and risk of fetal anomalies

- Adverse outcomes associated with DM in pregnancy
  - Preeclampsia
  - Hydramnios
  - Macrosomia/ large for gestational age (LGA)
  - Fetal organomegaly (hepatomegaly, cardiomegaly)
  - Maternal and infant birth trauma
  - Operative delivery
  - Perinatal mortality
  - Neonatal respiratory problems and metabolic complications (hypoglycemia, hyperbilirubinemia, hypocalcemia)



If the mother is **hyperglycemic during organogenesis, the risks of **miscarriage** and **congenital anomalies** are increased.

IAb+ Adults and Pregnancy

Goal: Avoid a missed early diagnosis of T1D to ensure normal fetal development.

Monitoring frequency in pregnancy for women with IAb⁺ status

- Women who are IAb⁺ and become pregnant should have an OGTT or HbA1c test or application of CGM soon after pregnancy is confirmed (by 8 weeks if possible) (18,106). **[B]**
- If diabetes is diagnosed based on OGTT, HbA1c or CGM data, starting insulin should be strongly considered (rather than diet adjustment alone or oral therapy with metformin, glyburide) if glucose values are consistent with Stage 3 T1D. **[E]**
- Women who are IAb⁺, and not already diagnosed with diabetes mellitus, should receive OGTT tests at 24-28 weeks as standard for all pregnancies. **[A]**
- Glucose monitoring for IAb⁺ women diagnosed with diabetes mellitus: once post-partum, women should be assessed prior to discharge from hospital, in consultation with a specialist endocrinologist, to determine continued need for insulin. **[B]**
- Women with IAb⁺ status should be monitored for 6-12 months post-partum to assess any changes in insulin requirement. **[E]** Where available, follow-up both with the gestational care provider and a diabetes-care initiation specialist should be provided. **[E]**

Monitoring in Adults: Unmet Needs

- More data/research in adult population
- Rates of progression to stage 3 T1D in IAb+ individuals without a family history of T1D (especially non-European ancestry)
- Cost effectiveness of monitoring strategies
- Implications of single IAb+ status in adults, implications for LADA
- ICD-10 codes – in progress!

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JDRF Guidance Document: Adult Sub-Group

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Thank you!

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