What are the benefits, harms, and available methods for type 1 diabetes islet autoantibody screening?

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Formerly JDRF

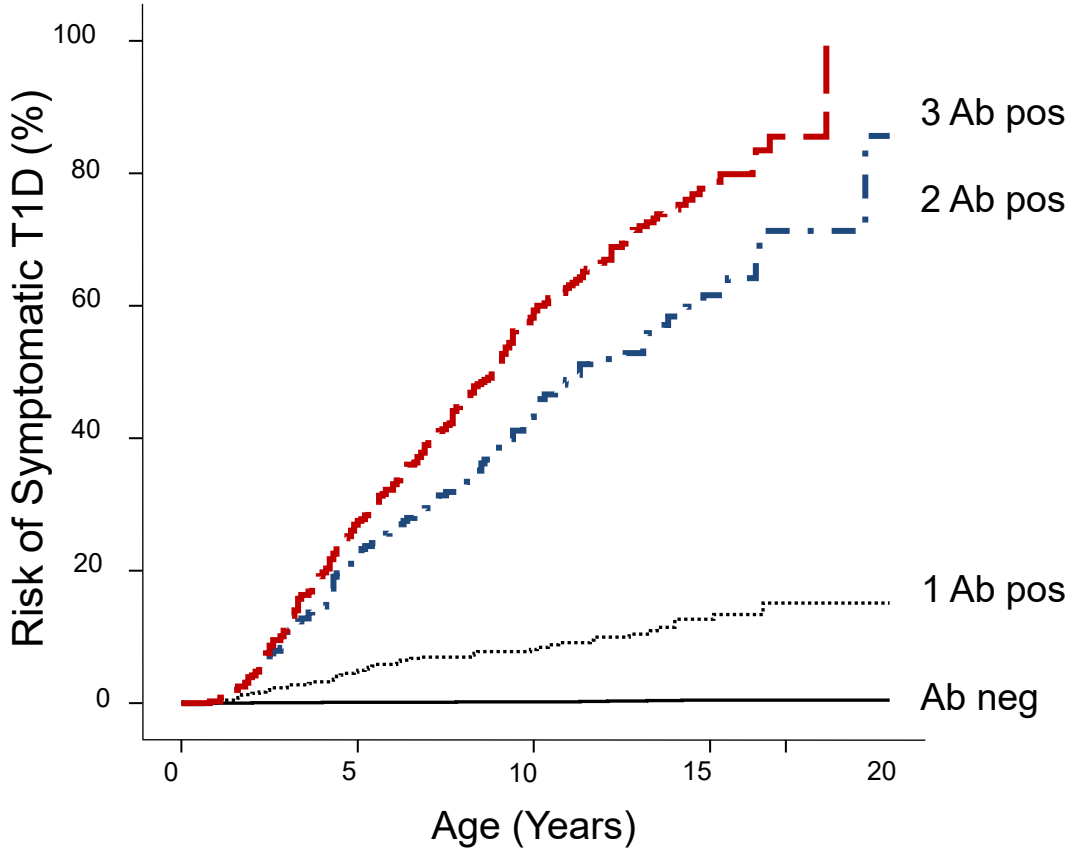
Conflicts of interest

MR: Serves on the advisory panel for Sanofi, Vertex. Received education grants from Sanofi.
All financial compensation for these activities has been received by the University of Colorado.

Benefits of screening for early stage T1D: Prior to clinical diagnosis

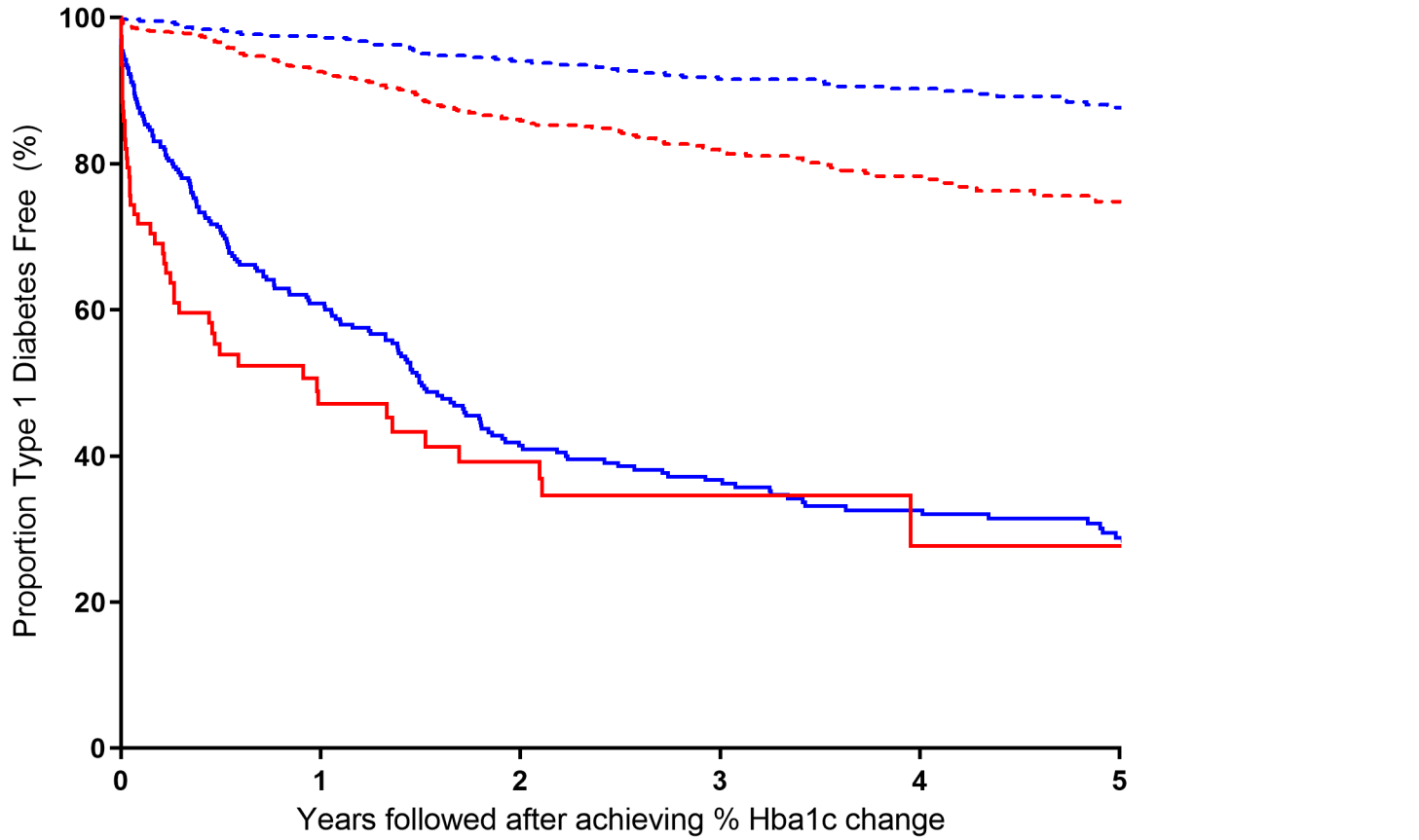
- Access to **gradual tailored diabetes management education** for IAb positive individuals and their families - time to plan and prepare "soft landing"
- Opportunity to receive **approved disease-modifying therapy** to delay disease progression
- Opportunity to participate in **clinical trials of novel interventions** to stop or slow progression to insulin dependence
- **Metabolic monitoring** helps predict time to clinical diagnosis

The Number of Islet Autoantibodies Predicts Progression to Stage 3 T1D



Ziegler, Rewers, Simell, JAMA 2013

Δ% HBA1C PREDICTS T1D IN RELATIVES (TRIALNET) CHILDREN AND TEDDY (RELATIVES AND GENERAL POPULATION)



N at risk

446	413	361	309	268	228	<10% TEDDY
261	146	90	77	58	46	≥10% TEDDY
1110	693	457	304	179	84	<10% TrialNet
80	28	18	13	5	2	≥10% TrialNet

- ≥10% change from baseline ↑ risk of progression in TrialNet and TEDDY children (independent of known risk factors)

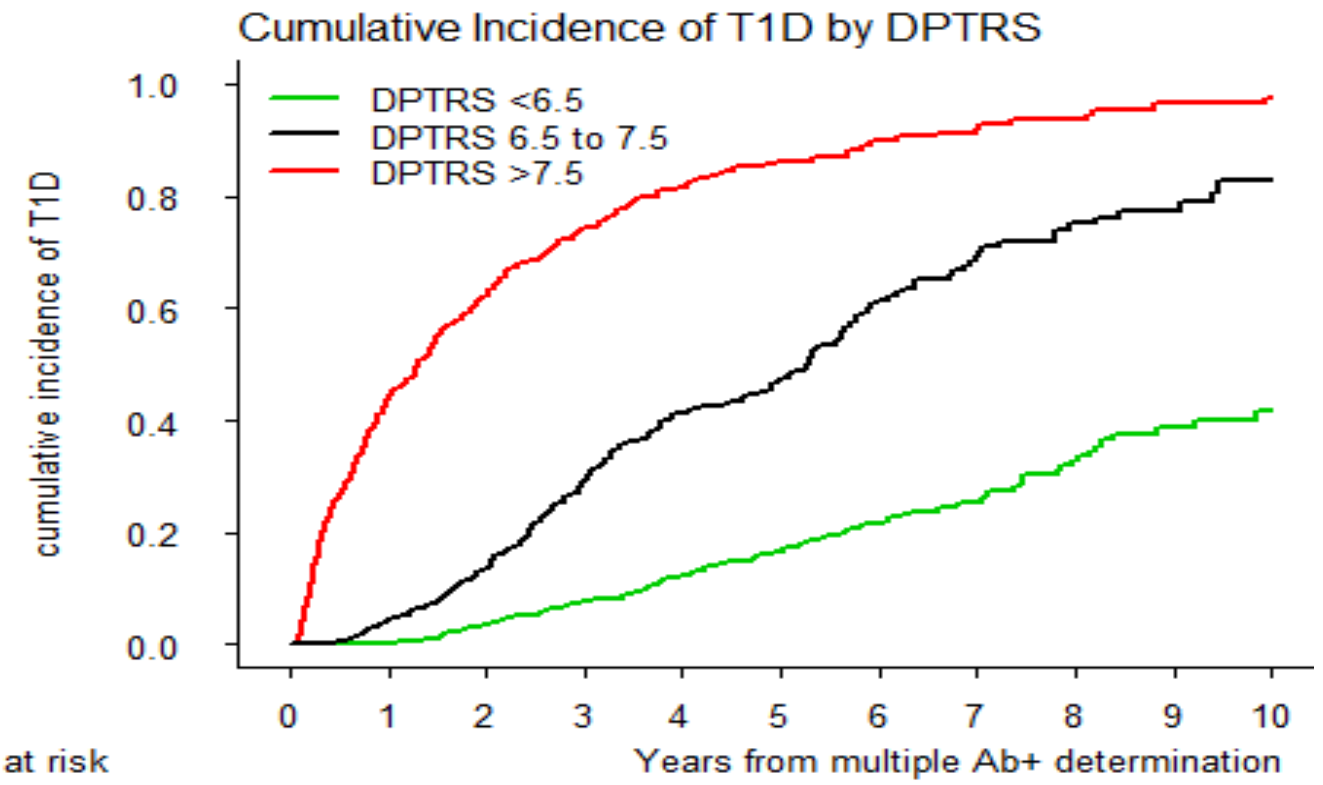
  TrialNet: ≥10% relative change ↑ risk 5-fold

  TEDDY: ≥10% relative change ↑ risk 12-fold

Vehik K, et al. Diabetes Care. 2022 Oct 1;45(10):2342-2349

PROGRESSION TO TYPE 1 DIABETES

By DPTRS (Glucose, C-peptide, age, BMI)



N at risk											
DPTRS <6.5	1490	866	585	415	303	217	153	118	76	47	33
DPTRS 6.5 to 7.5	923	501	343	210	137	97	57	37	22	14	8
DPTRS >7.5	738	282	148	84	47	30	16	10	7	4	3

Type 1 Diabetes TrialNet

Benefits of screening for early stage T1D: At clinical diagnosis and later

- **Prevention of DKA** at diagnosis of clinical T1D and its acute neurologic, vascular, and kidney complications.
- **Prevention of hospitalization** at diagnosis, reduction of the associated direct and indirect cost.

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Screening, monitoring and education can prevent DKA at onset

Study	Frequency of DKA	Reference
Children identified through general population screening programs		
Frlda (Germany)	**5.6%**	Ziegler A-G. JAMA 2020
Autoimmunity Screening for Kids ASK (Colorado)	**4.5%**	Rewers M. EASD 2024
Children diagnosed without prior screening		
Sweden **Finland** **Germany**	**22%** **23%** **24%**	Wersäll J. Pediatr Diabetes 2021 Hekkala A. Pediatr Diabetes 2018 Kamrath C. JAMA 2020
USA (SEARCH) 2010 - 2016 **Colorado 1998 → 2012** **Colorado 2010 → 2017** **Colorado 2017 - 2019**	**41%** **30% → 46%** **41% → 58%** **52%** **62%**	Jensen E. Diabetes Care 2021 Rewers A. JAMA 2015 Alonso G. Diabetes Care 2020 Alonso G. Diabetes Technol Ther 2021 Alonso G. Diabetes Technol Ther 2021

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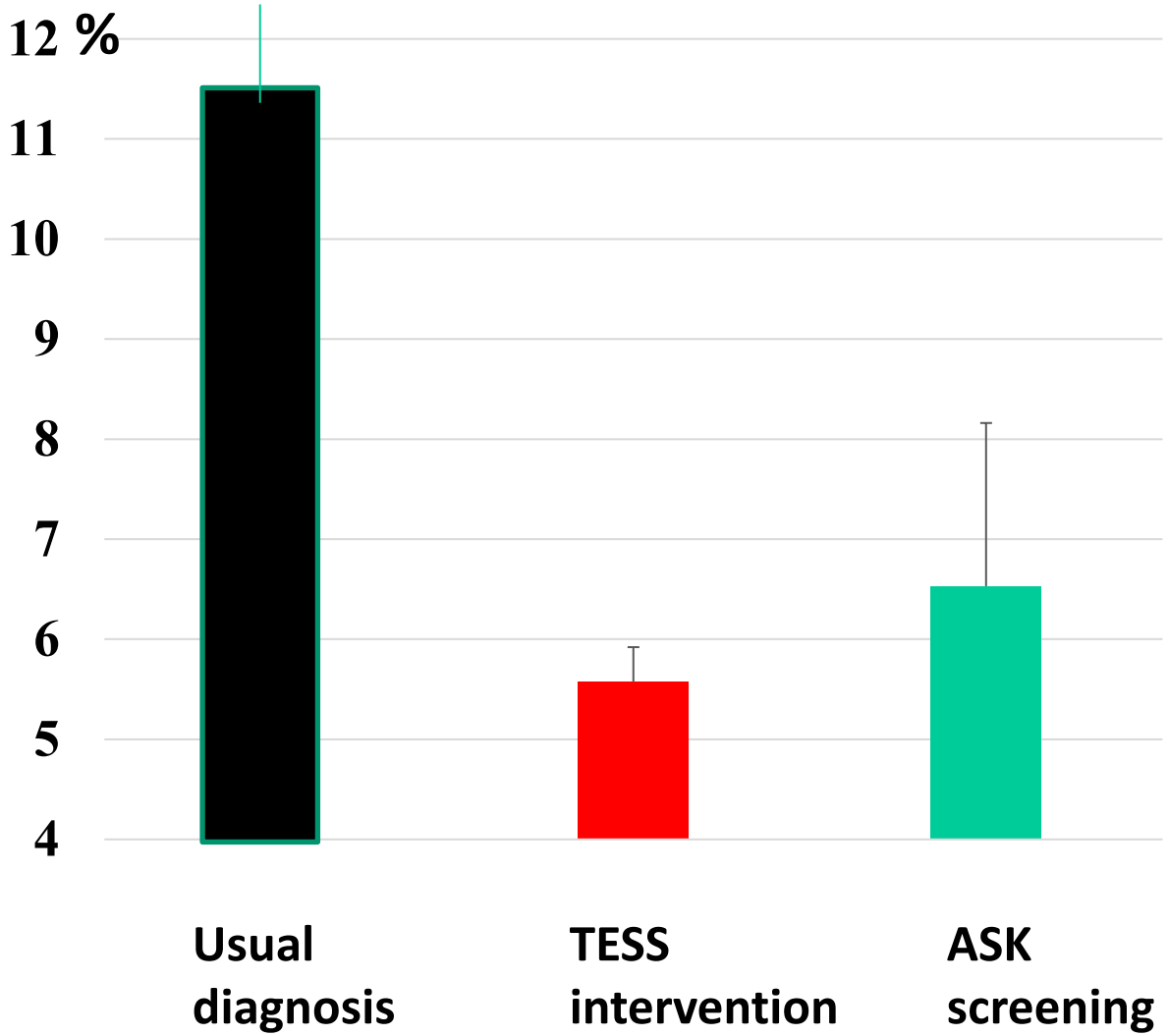
- Early diagnosis leads to **milder disease on clinical presentation** with lower HbA1c and greater C-peptide.

HbA1c at Diagnosis in The Early Start Study



Intervention (6 months):

- Unblinded CGM-guided education
- 3 planned educational visits
- Monthly check-in to review CGM
- CGM-guided insulin start

tess THE EARLY START STUDY FOR PRE-SYMPTOMATIC T1D

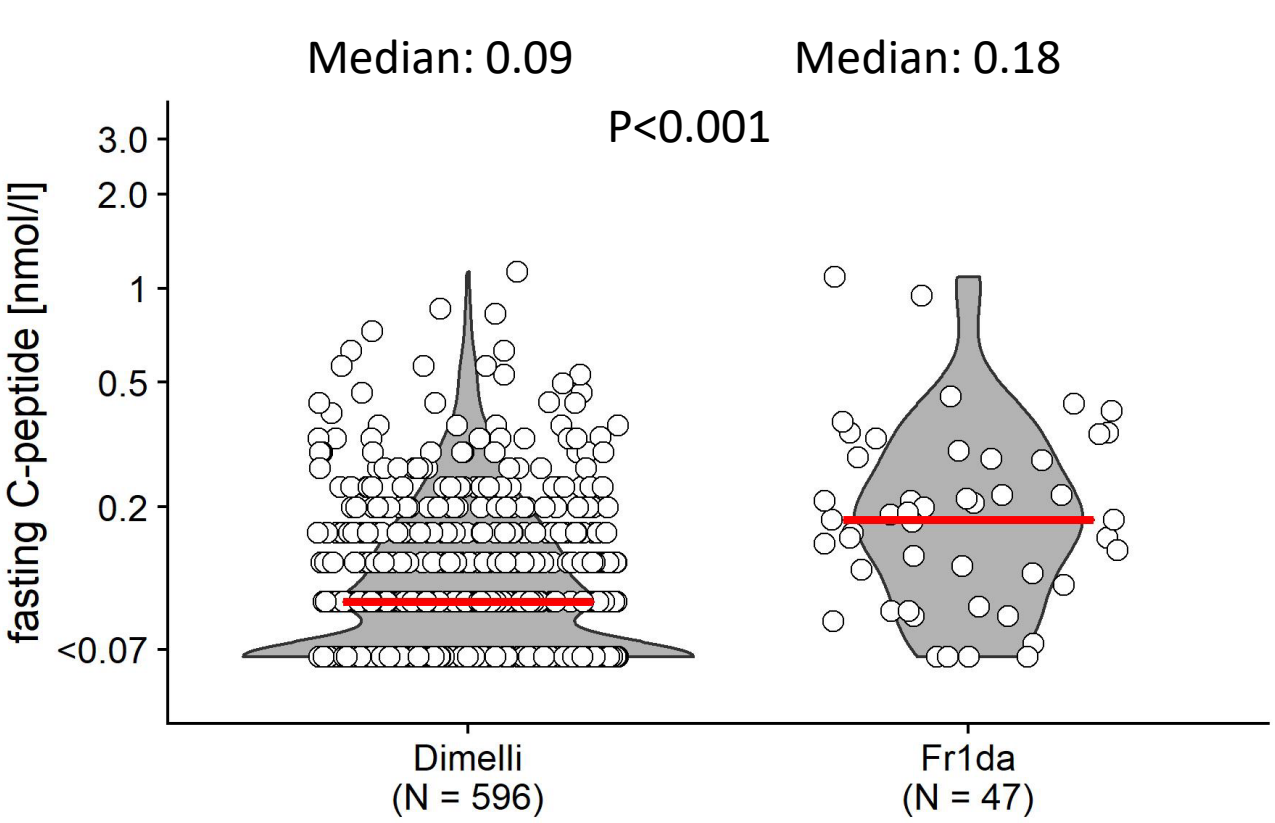
Autoimmunity Screening for Kids ask

courtesy: Brigitte Frohnert, MD, PhD

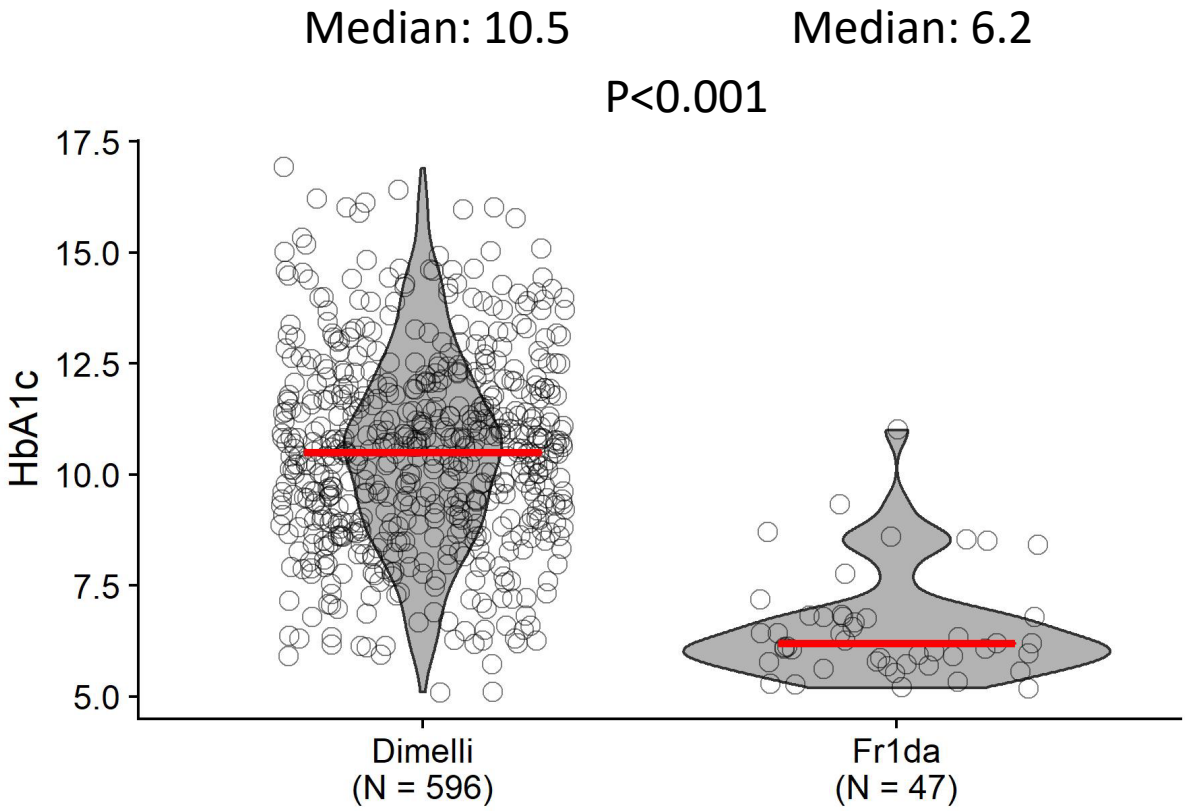
More beta-cell function at clinical diagnosis

Fr1da
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Fasting C-Peptide at clinical manifestation



HbA1c at clinical manifestation



DiMelli
Studie zur Untersuchung von neu aufgetretenem **Diabetes mellitus** im Kindes- und Jugendalter

New onset register cohort in children in Bavaria, Germany

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- Early diagnosis leads to **milder disease on clinical presentation** with lower HbA1c and greater C-peptide.
- Early detection and control of hyperglycemia **improves long-term metabolic control** and decreases the risk of complications.

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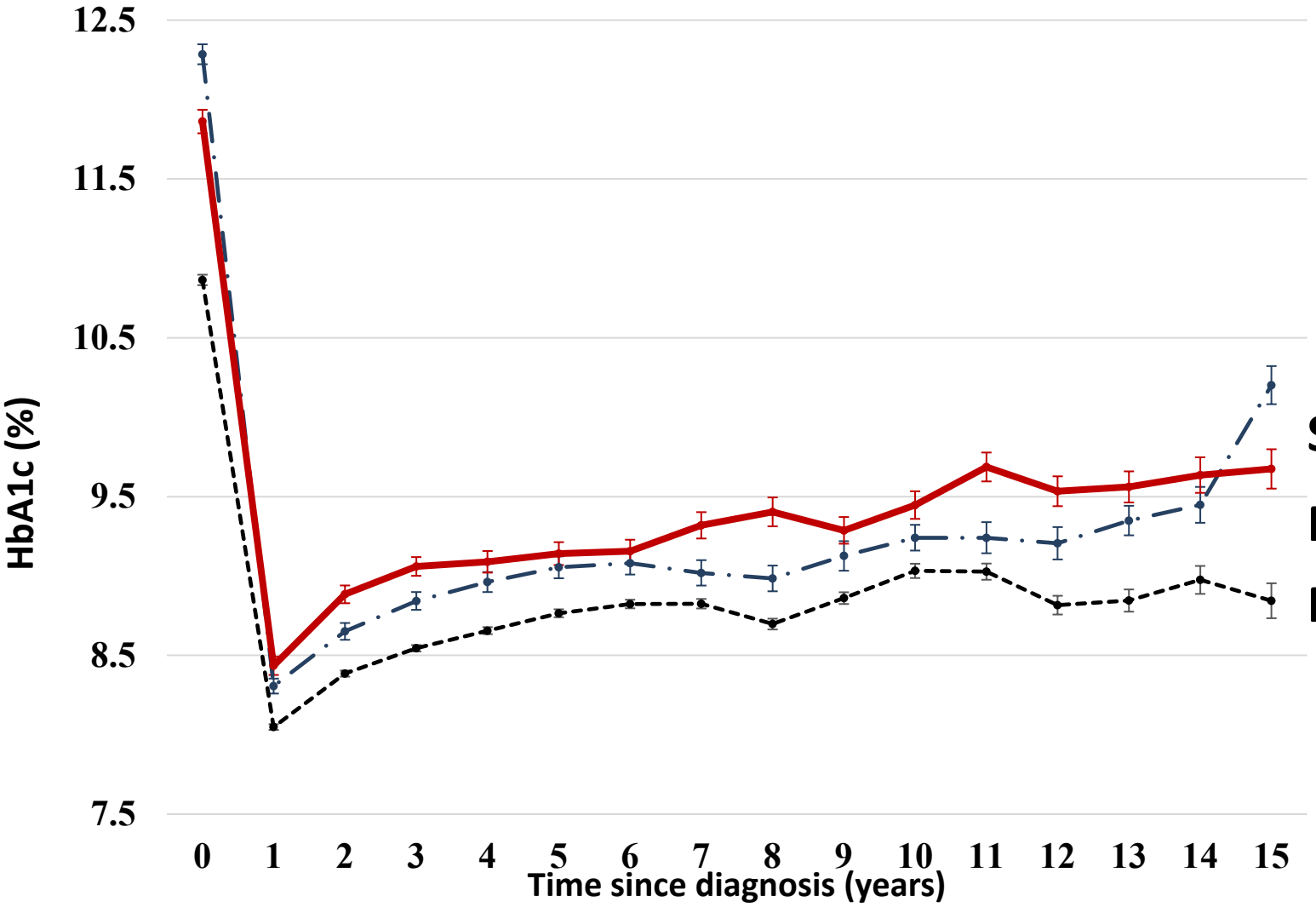
DKA at diagnosis predicts worse long-term A1c

3364 Colorado children, BDC patients, followed for up to 15 yrs



Severe DKA A1c ↑ 1.4% p<0.0001

Mild/moderate A1c ↑ 0.9% p<0.0001

No DKA

Adjusted for age, sex, race/ethnicity, family Hx insurance, insulin pump treatment

Duca L et al. Diabetes Care 2017

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- Early diagnosis leads to **milder disease on clinical presentation** with lower HbA1c and greater C-peptide.
- Early detection and control of hyperglycemia **improves long-term metabolic control** and decreases the risk of complications.
- **Improved quality of life** of affected children and their relatives at the time of clinical diagnosis and following initiation of insulin therapy.

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Potential harms and mitigation strategies

Potential Harm	Mitigation Strategy
Blood sampling can be painful and cause bruising	Topical anesthetics
Psychosocial impact - awareness of early-stage T1D may induce anxiety	Decreases over time with participation in an informative monitoring program
A false-positive test result – this can cause anxiety and depression, even if corrected	Highly specific islet autoantibody assays minimize false-positivity
False reassurance following a negative screens	Clear guidance and information
A diagnosis of early-stage T1D can cause stigma	Community education

Costs of Screening

To participating families

Loss of caregiver income due to increased health care utilization for monitoring. education to prevent DKA and hospitalization.

Potential problems with health insurance, credit ratings, and job prospects.

To healthcare system

Education of health care providers. Provider time to complete screening and confirmation.

Laboratory cost of screening and confirmation.

Results notification, explanation and documentation in health medical records.

Monitoring for development of dysglycemia and progression to hyperglycemia.

Psychosocial support for families with increased anxiety.

Raising community awareness about benefits of screening, information materials.

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Recommendations related to assay selection
VALIDITY

The IAb detection assay protocols for general population screening for early-stage T1D must mitigate against high numbers of false positive and false negative tests.[B]
The selected IAb assays should be certified and validated for use outside of the research study context.[E]

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Assays available for T1D autoantibody screening

Assay modality	Advantages	Disadvantages
Radiobinding assay (RBA)	'Gold standard' with established standard protocols and performance High sensitivity Low serum volume required for GADA, IA-2A, ZnT8A Reagents generally freely available without commercial licensing Semi-automation can achieve high throughput	Higher sample volume required for IAA Requires radioisotopes and associated regulation and, therefore, only likely to be available in large institutions with existing licenses. Increased cost from required frequent radiolabeled autoantigen production and from the lack of full automation. Not easily multiplexed
Bridge Enzyme-linked immunosorbent assay (ELISA)	High sensitivity Low to moderate serum volume Commercially available Used in several research screening programs Amenable to high-throughput automation	Does not include IAA Multiplex assay does not distinguish which antibody is positive

Assays available for T1D autoantibody screening

Assay modality	Advantages	Disadvantages
Electrochemiluminescence (ECL) Bridge assay	High sensitivity Low serum volume Commercially available Amenable to high-throughput automation Multiplex potential to screen and identify all 4 IAb	Reliance on proprietary commercial reagents and instrumentation increases cost
Antibody Detection by Agglutination-PCR (ADAP)	High sensitivity Low serum volume or dried blood spot Commercially available Amenable to high throughput Multiplex potential to screen	Reliance on proprietary commercial reagents and instrumentation increases costs
Luciferase immunoprecipitation (LIPS)	High sensitivity Low serum volume Amenable to high-throughput automation	Not commercially available Relies on in house reagents that are less widely available and likely need individual lab standardization Multiplex assay does not distinguish which antibody is positive

Recommendations related to assay selection CONFIRMATION

When IAb are detected during screening, confirmation with a second blood sample is required.[B]
Confirmatory testing should ideally use a different assay method from that used in the initial screening test, when available.[E]
At the point of confirmation, the diagnosis of early-stage T1D must have a high degree of confidence in the IAb detection assay protocols and procedures employed.[B]

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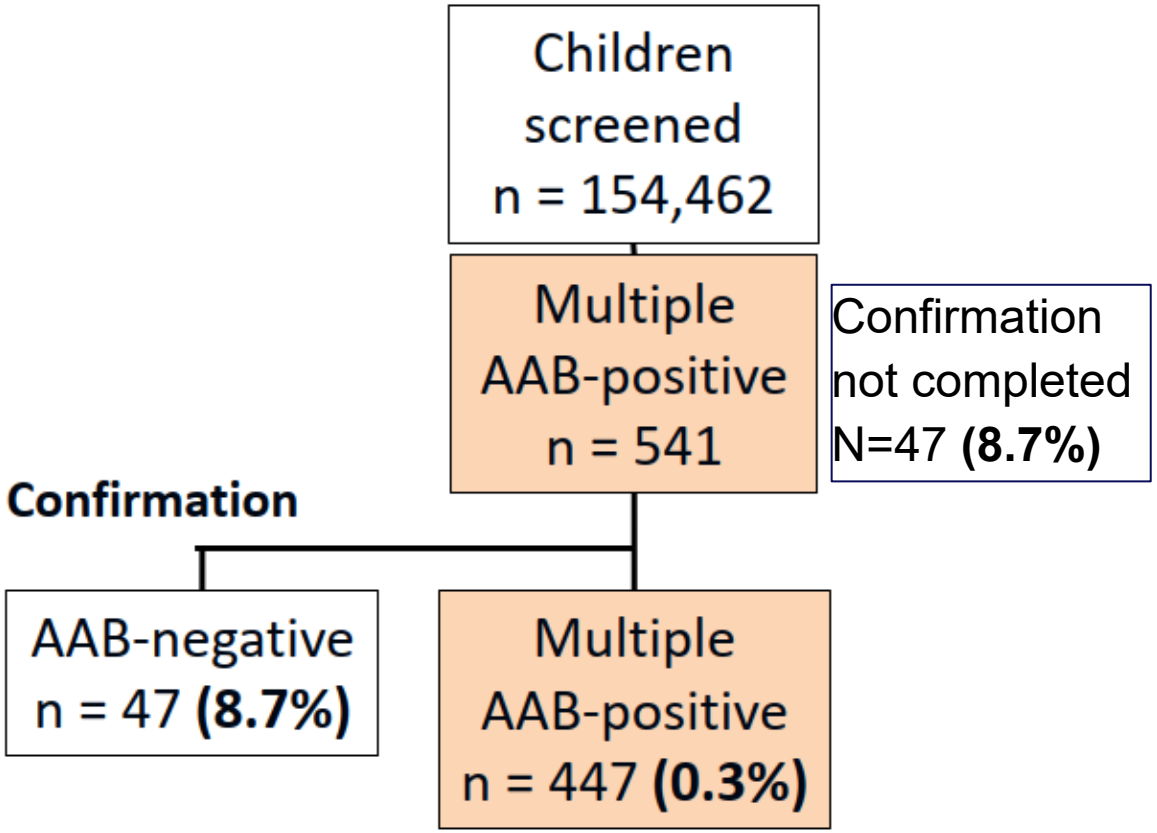
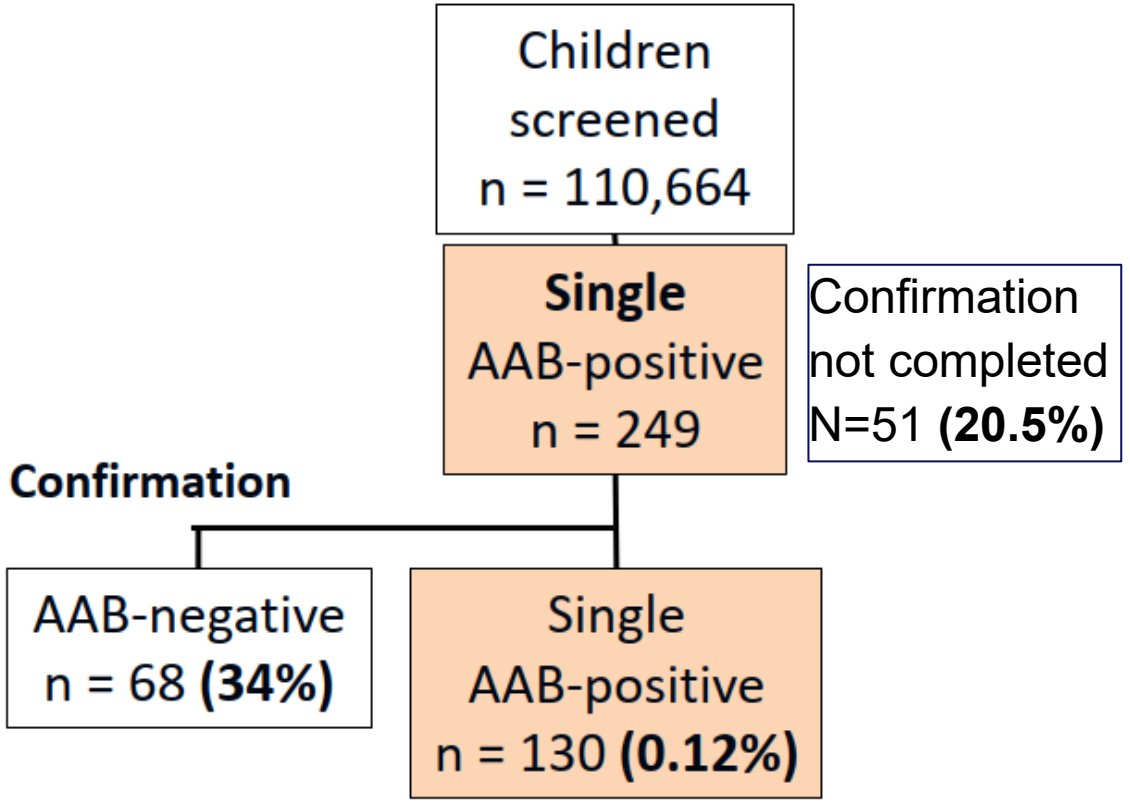
Importance of Confirmation

Fr1da results: 9% of multiple IAb and **34%** of single IAb were negative at confirmation





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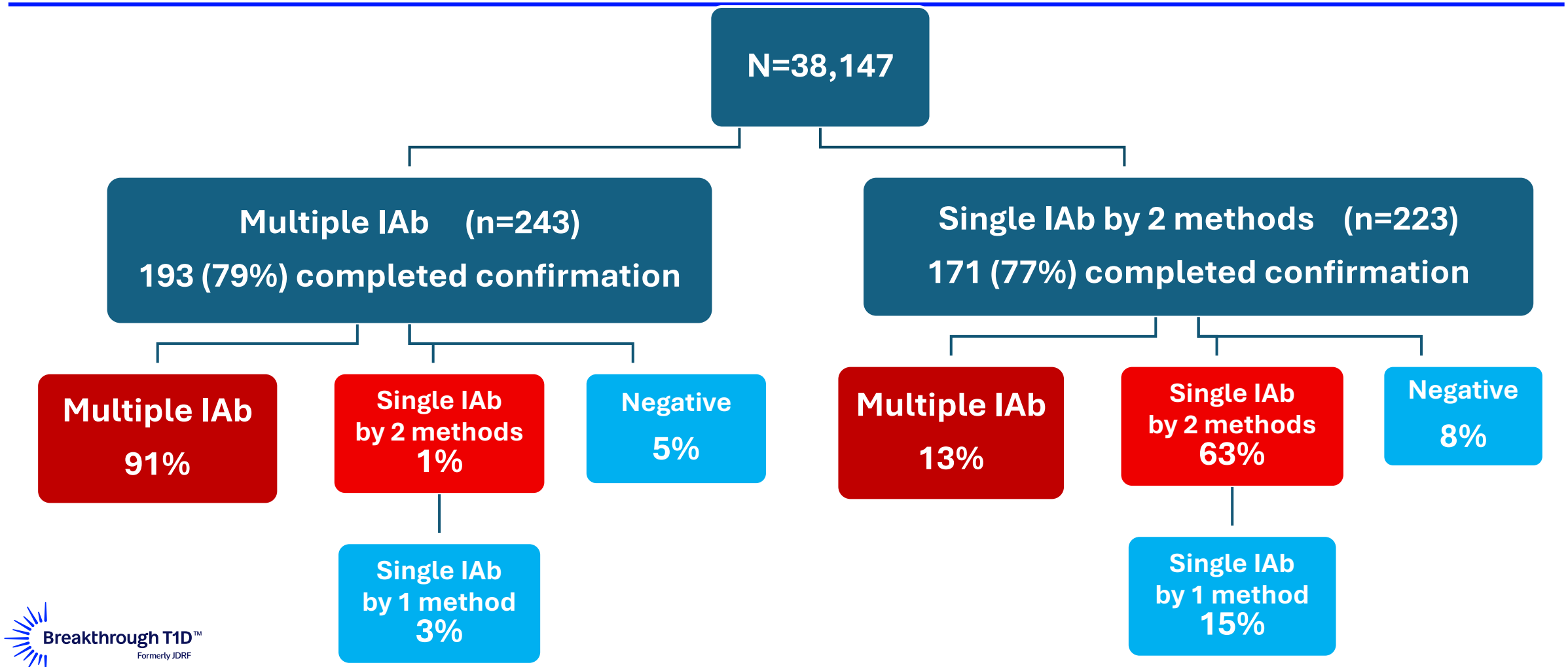
JAMA 2020, Diabetologia 2022, EASD 2025

Importance of Confirmation

ASK results: **8%** of multiple IAb and **23%** of single IAbs were negative at confirmation



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ASK Protocol

SCREENING

5-plex ECL:

IAA, GAD, IA-2, ZnT8

& tTG

Reflex RBA confirmation of positives

Negative

CONFIRMATION

Repeat 5-plex ECL

RBAs: IAA, GAD, IA-2, ZnT8

Islet autoantibodies:

- multiple

- single by 2 methods (high-affinity)

Recommendations related to assay selection

Test sample collection and delivery to a clinical laboratory should maximize participation and promote equitable access to screening among underserved groups based on socioeconomic status, geography, or ethnicity.[C]

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Screening, Confirming and Retaining in Monitoring

- Racial and ethnic minorities, recent immigrants
- Families deprived of primary health care or health insurance
- Families with fewer years of formal education
- Families with lower socioeconomic status
- Inner city and rural residents