How is precision medicine changing the paradigm in type 1 diabetes?

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KU LEUVEN

Speaker disclaimer

CM serves or has served on the advisory panel for Abbott, Bayer, Biomea Fusion, Boehringer Ingelheim, Dexcom, Eli Lilly and Company, Insulet, Medtronic, Novartis, Novo Nordisk, Roche, SAB Bio, Sanofi, and Vertex.

Financial compensation for these activities has been received by KU Leuven;

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KU Leuven has received research support for CM from Dexcom, Novo Nordisk and Sanofi.

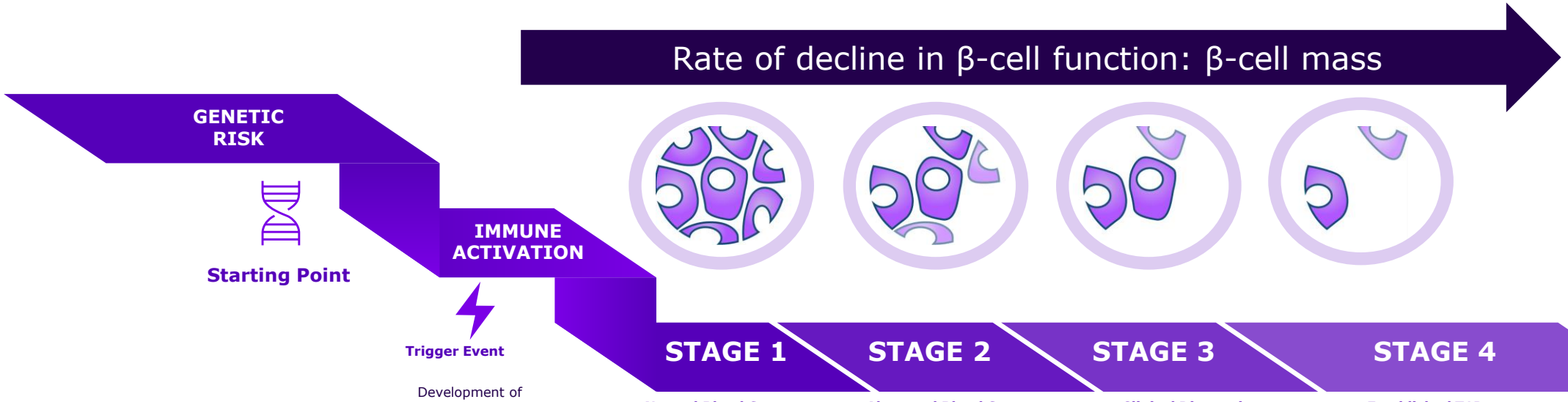
CM is president of EASD.

All external support of EASD is to be found on www.easd.org.

What is precision medicine…?

https://www.efpia.eu/about-medicines/development-of-medicines/precision-medicine/ Accessed September 28th 2025

T1D: Stages of disease

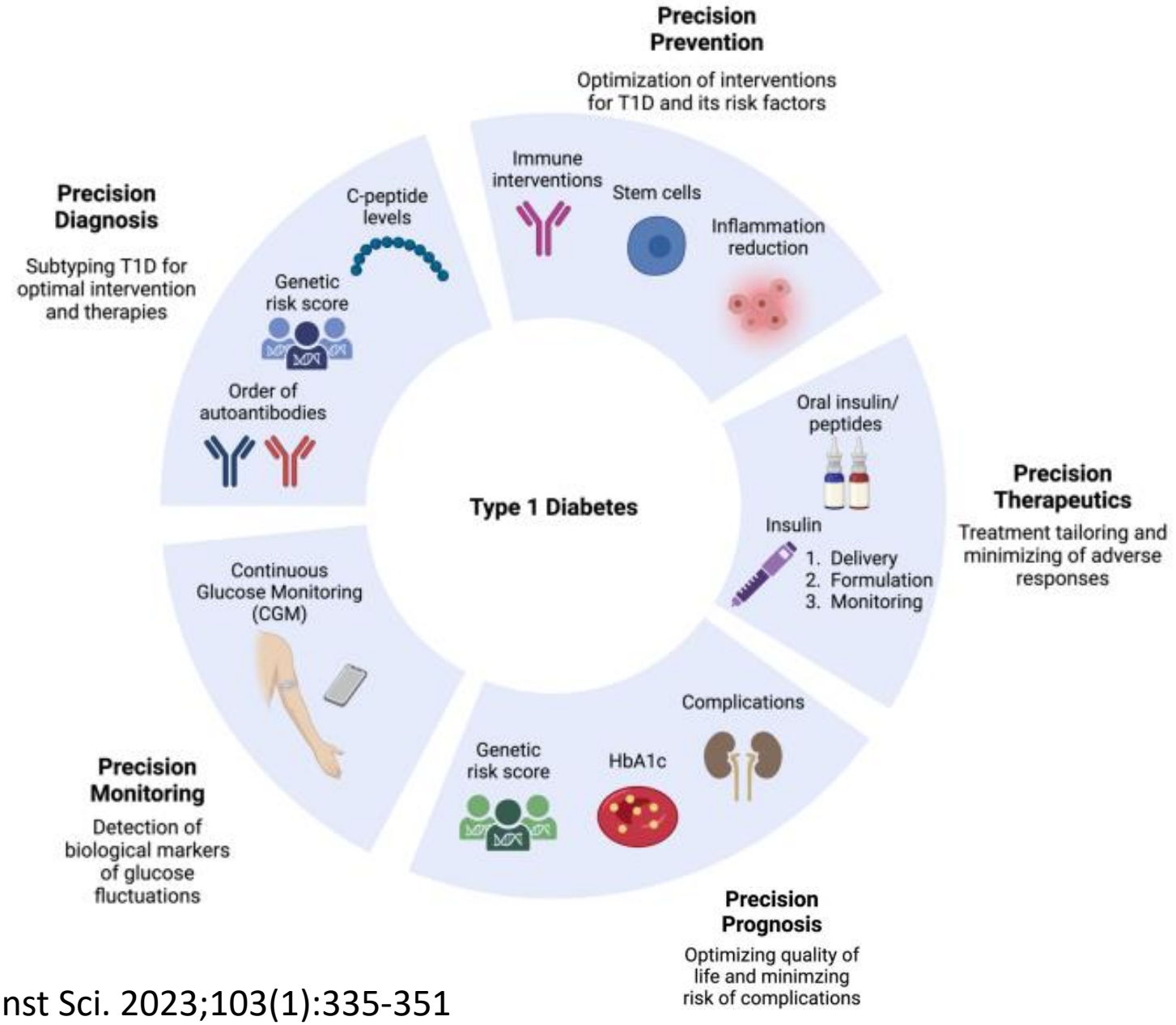


	STAGE 1	STAGE 2	STAGE 3	STAGE 4
	Development of single autoantibody	**Normal Blood Sugar** ≥ 2 autoantibodies	**Abnormal Blood Sugar** ≥ 2 autoantibodies + dysglycemia	**Clinical Diagnosis** Based on ADA criteria for diagnosis of diabetes	**>Established T1D**
Pathophysiology:		Identifies individuals who have developed a broad autoimmune response against multiple islet autoantigens and will eventually progress to clinical disease	β–Cell dysfunction, defined based on dysglycemia, can be identified using provocative testing (e.g., oral glucose tolerance tests)	At the time of diagnosis, there is still β-cell reserve with clinical significance in terms of glycemic control and avoidance of hypoglycemia	β–Cell function continues to decline with time after diagnosis
5-year risk of clinical diagnosis of T1D:		44%	75%	N/A	N/A

By the time people with T1D display symptoms, **β-cell mass is significantly reduced**

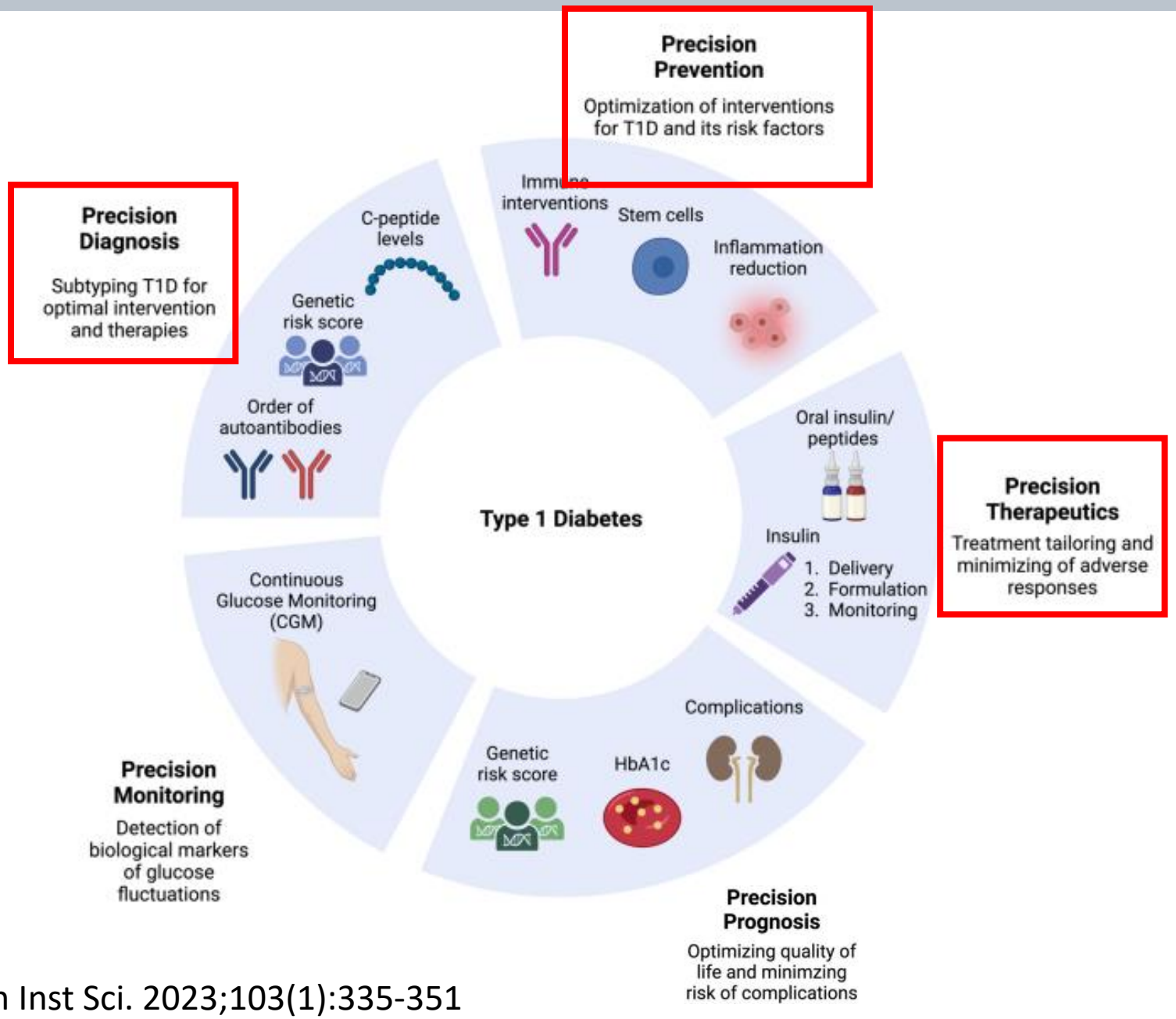
Sims EK, et. al. Diabetes 2022;71:610–3; Besser RE, et al. Pediatr Diabetes 2022;23:1175–87

Different aspects of precision medicine



Michalek DA et al J Indian Inst Sci. 2023;103(1):335-351

Different aspects of precision medicine



Michalek DA et al J Indian Inst Sci. 2023;103(1):335-351

Precision diagnosis

age

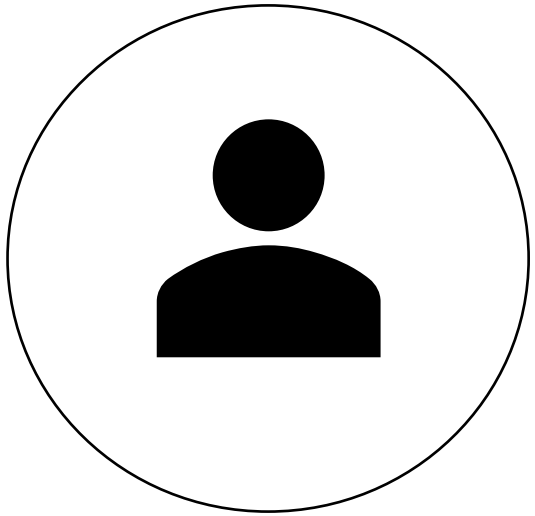
weight

blood pressure

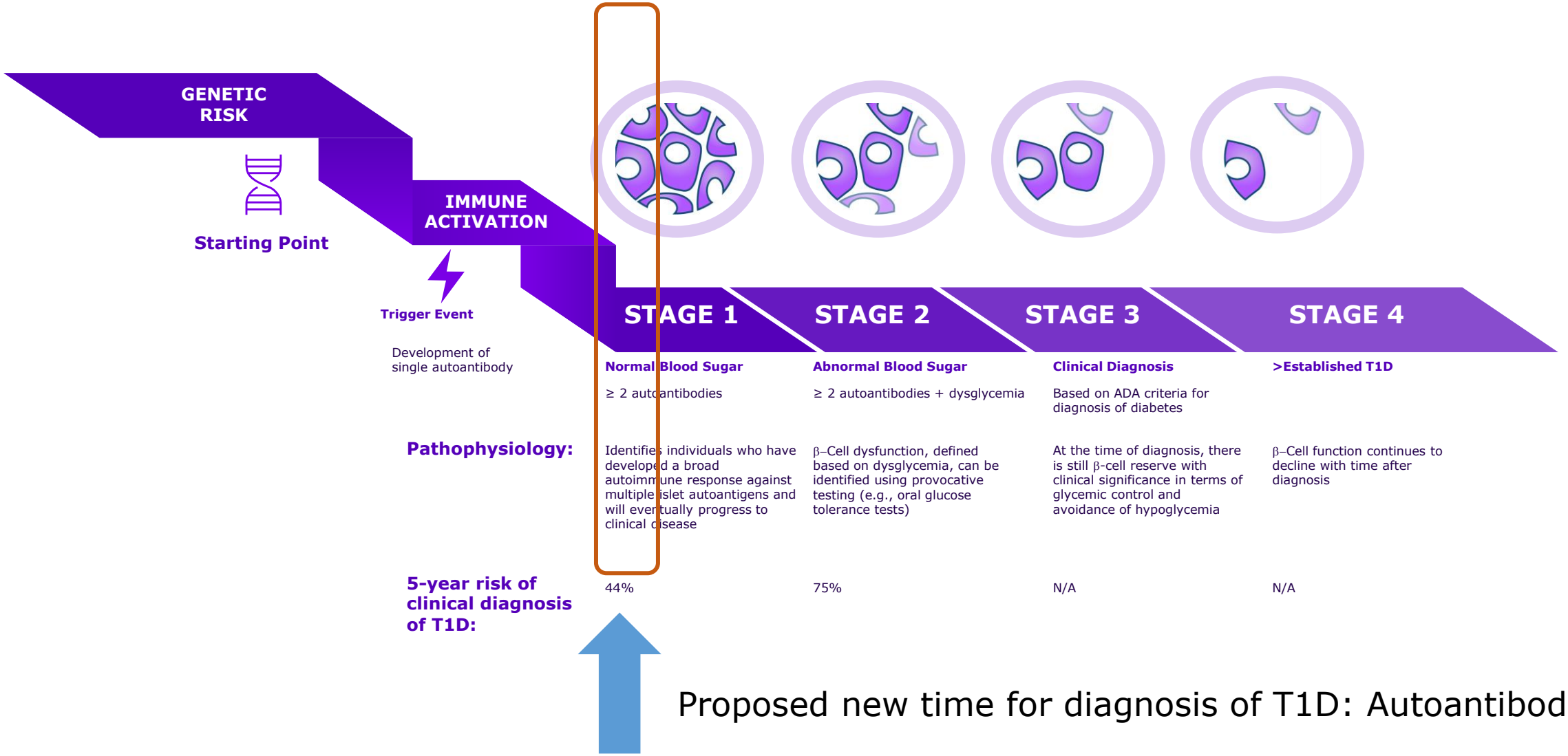
lipid profile

medication use

HbA1c



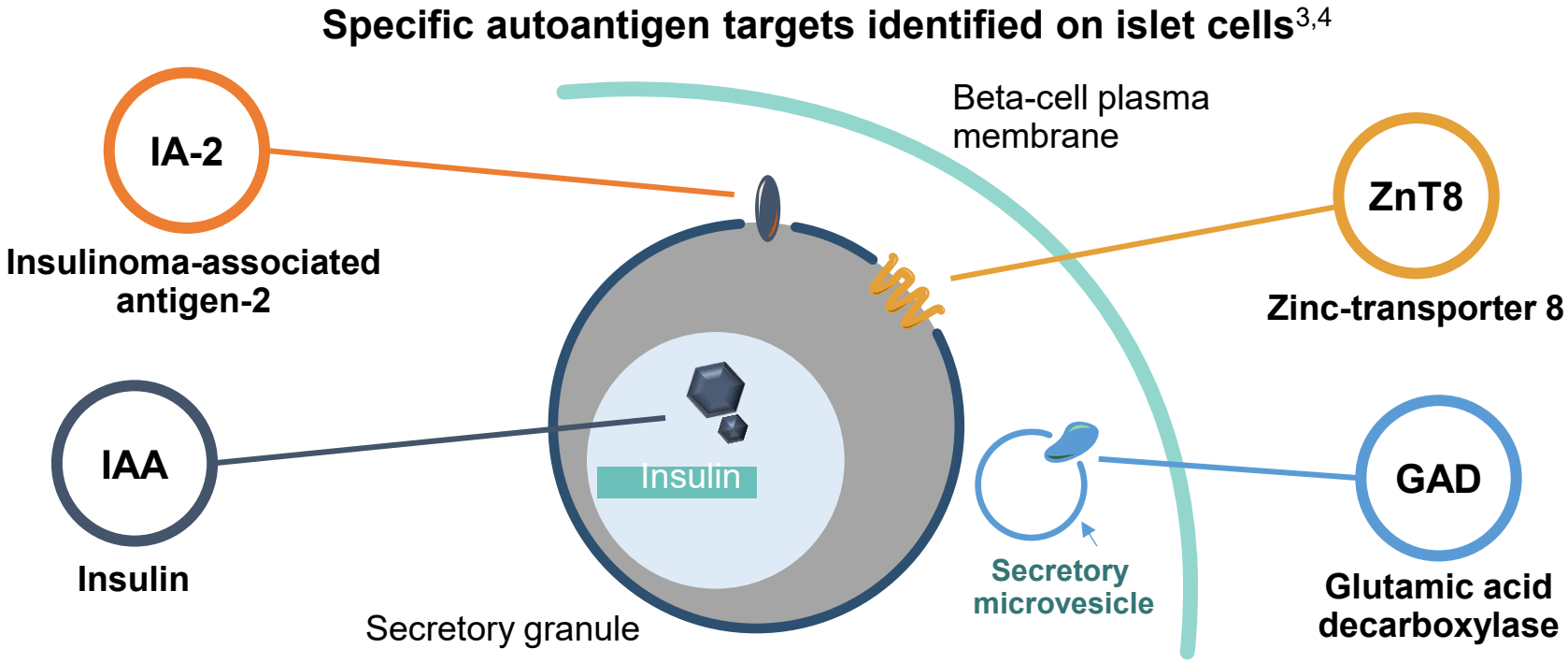
T1D: Time for change

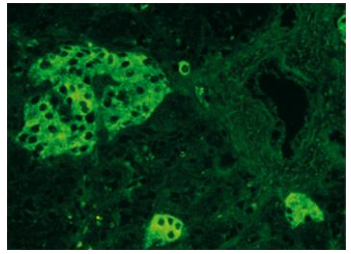


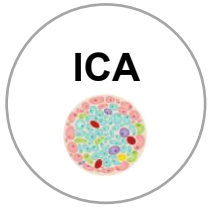
Proposed new time for diagnosis of T1D: Autoantibodies

Sims EK, et. al. Diabetes 2022;71:610–3; Besser RE, et al. Pediatr Diabetes 2022;23:1175–87

The ADA and ISPAD Recommend Screening for Islet Autoantibodies to Establish the Presence of Presymptomatic T1D







ICAs are not generally used for screening as they lack specificity and are technically challenging to detect[3,5]

Figure adapted from Arvan 2012[4]

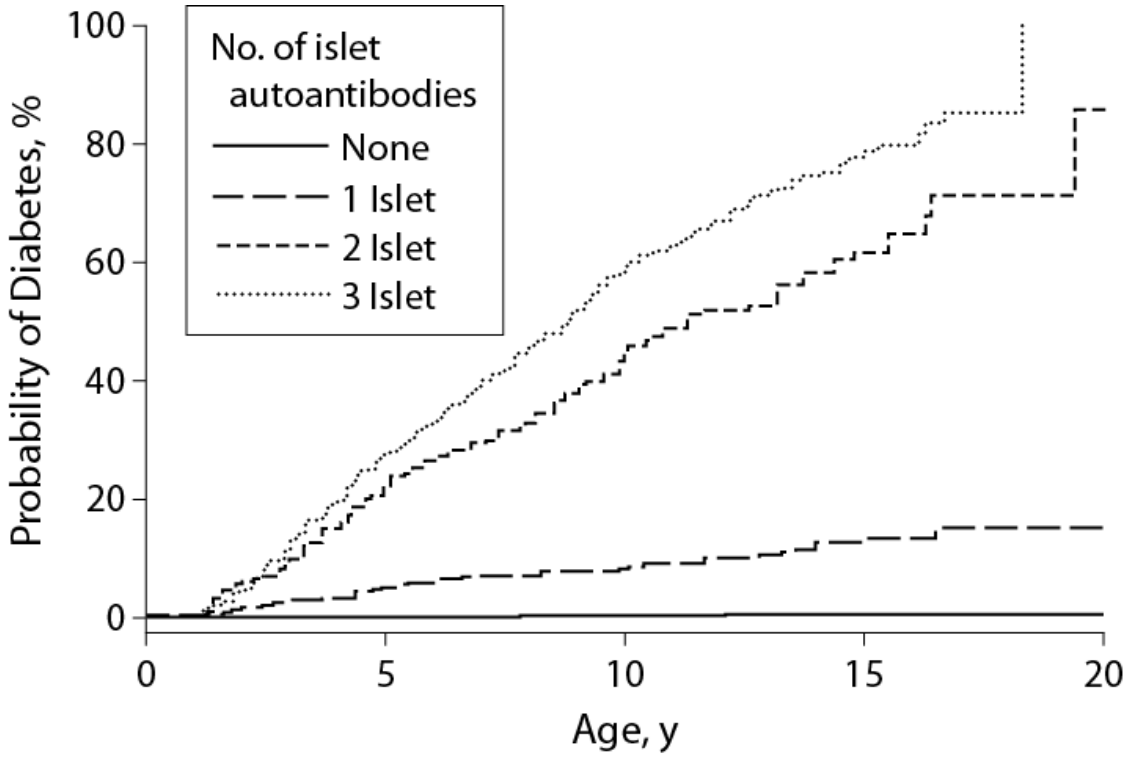
The presence of ≥2 confirmed islet autoantibodies identifies people with autoimmunity, many of whom may be **presymptomatic** (Stage 1 and 2) **and at a high risk of progressing to clinical aT1D** (Stage 3) over their lifetime[1]

ADA, American Diabetes Association; ICA, islet cell cytoplasmic autoantibody; ISPAD, International Society for Pediatric and Adolescent Diabetes; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; IAA, insulin autoantibody; T1D, type 1 diabetes; ZnT8, zinc-transporter 8.

1. American Diabetes Association Professional Practice Committee. Diabetes Care. 2024;47(Suppl. 1):S20-42. 2. Besser REJ, et al. Pediatr Diabetes. 2022;23(8):1175-87. 3. Winter WE, et al. J Appl Lab Med. 2022;7:197-205. 4. Arvan P, et al. Cold Spring Harb Perspect Med. 2012;2 a007658. 5. Peters A. J Fam Pract. 2021;70(6S):S47-52.

Biomarkers for an early diagnosis

risk of progression to symptomatic type 1 diabetes with **multiple islet autoantibodies** approaches 100%



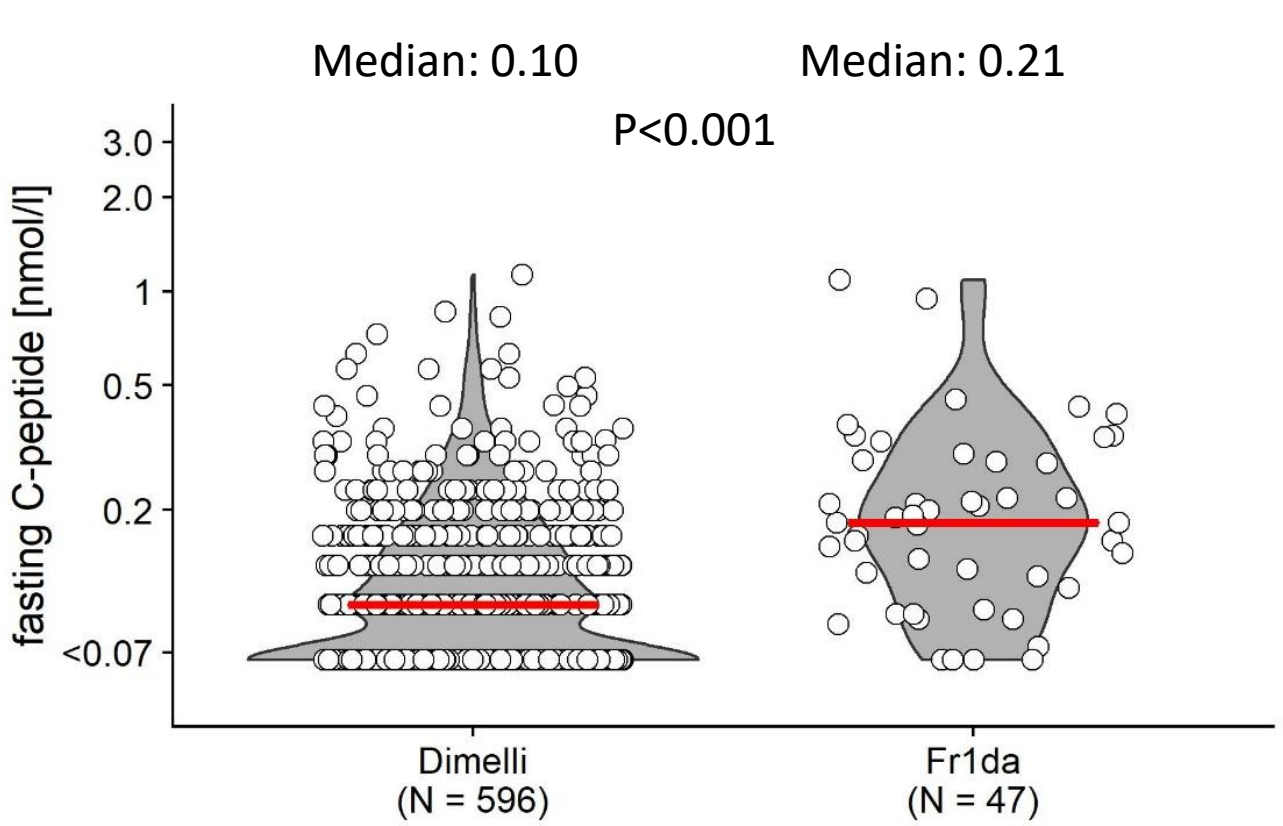
paradigm shift for staging of type 1 diabetes before clinical onset

Ziegler AG et al. JAMA 2013.

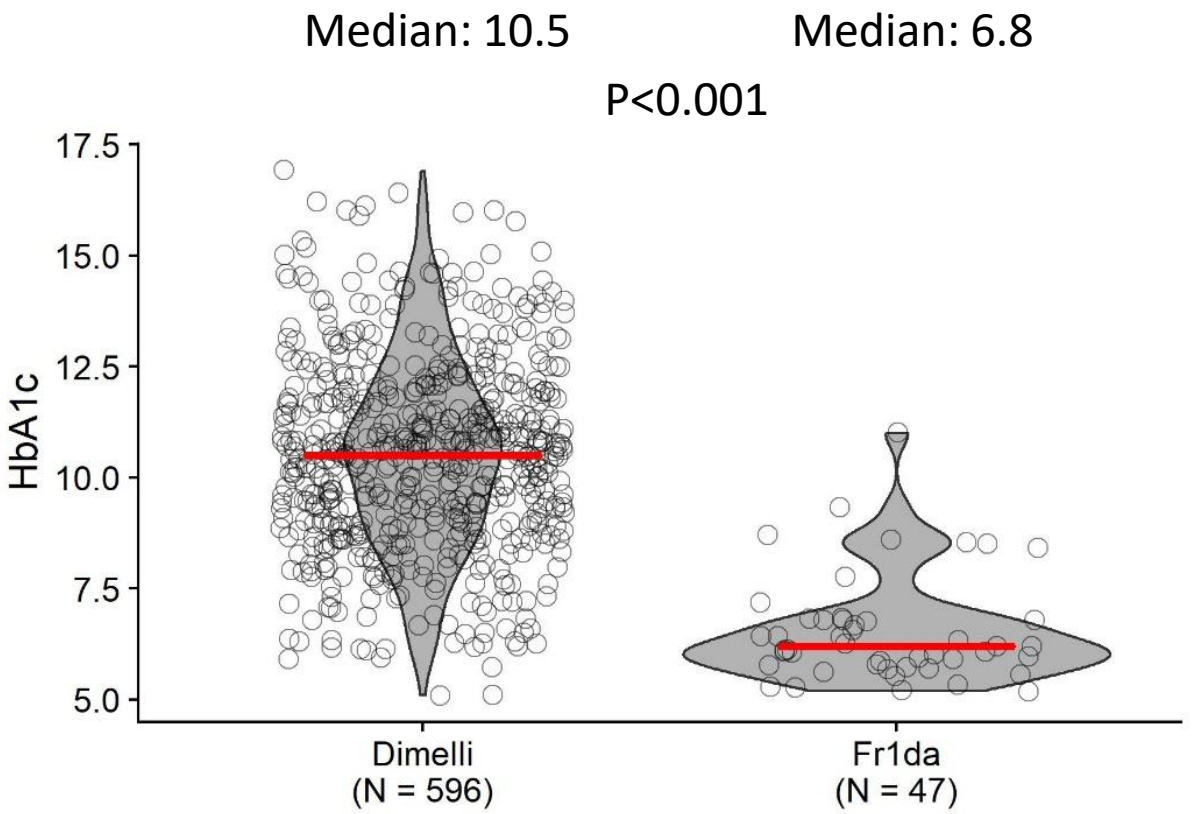
Children diagnosed with presymptomatic T1D through public health screening have milder diabetes at clinical manifestation

Fr1da
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Fasting C-Peptide at clinical manifestation



HbA1c at clinical manifestation

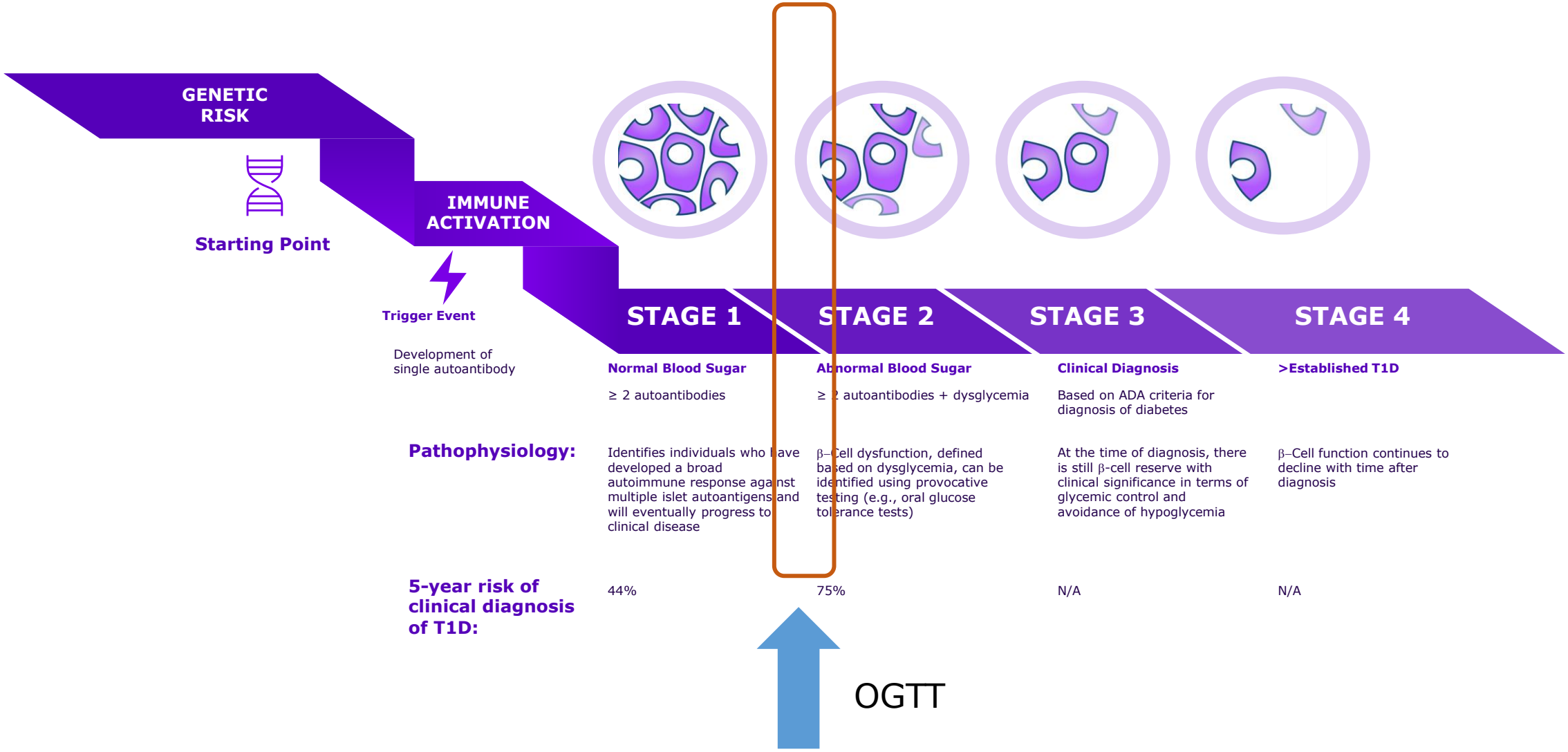


DiMelli
Studie zur Untersuchung von neu aufgetretenem Diabetes mellitus im Kindes- und Jugendalter

New onset register cohort in children in Bavaria, Germany

Hummel S et al. Diabetologia. 2023 Sep;66(9):1633-1642

T1D: Time for change

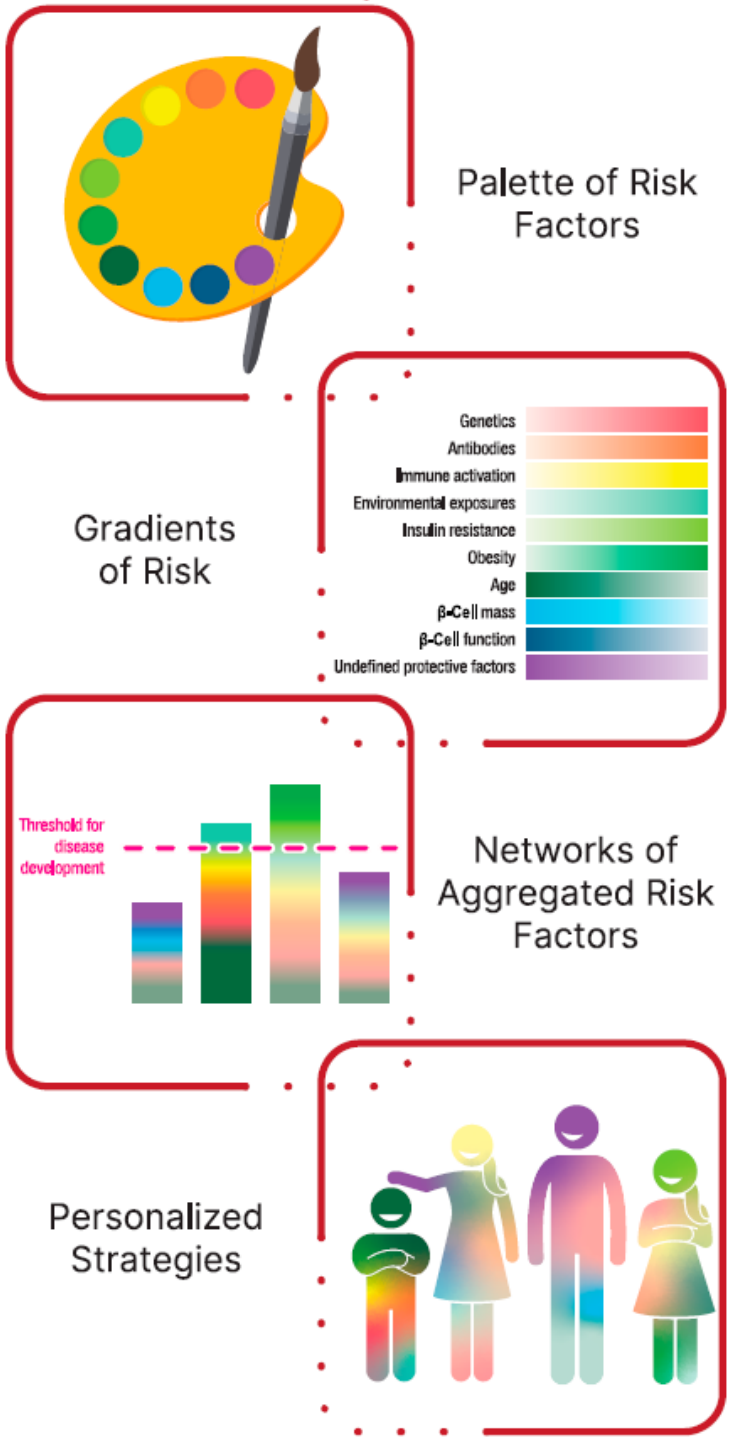


Sims EK, et. al. Diabetes 2022;71:610–3; Besser RE, et al. Pediatr Diabetes 2022;23:1175–87

The Heterogeneity of Type 1 Diabetes: Implications for Pathogenesis, Prevention, and Treatment—2024 *Diabetes*, *Diabetes Care*, and *Diabetologia* Expert Forum

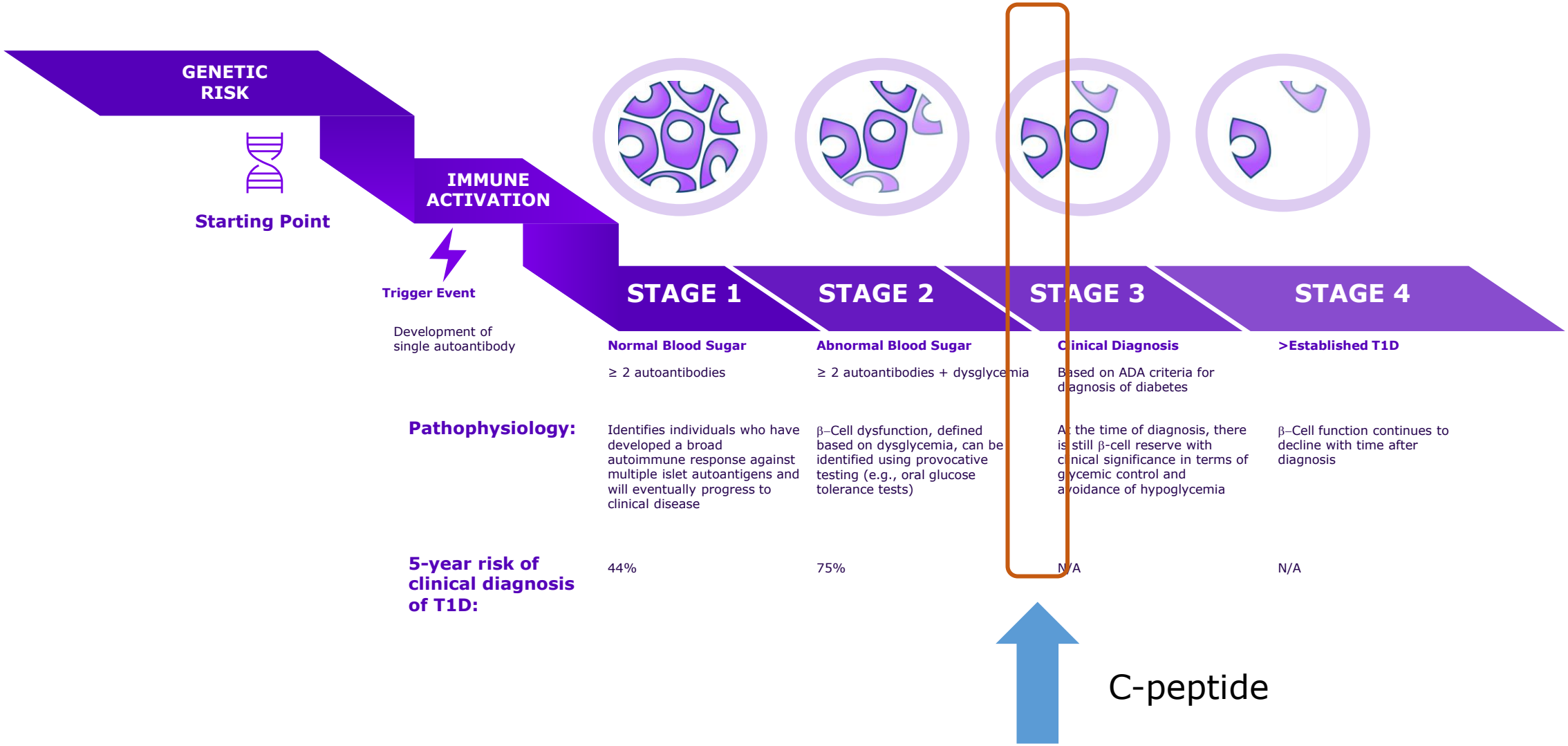
Carmella Evans-Molina,[1,2,3] Yuval Dor,[4] Åke Lernmark,[5] Chantal Mathieu,[6] Jeffrey R. Millman,[7] Raghavendra G. Mirmira,[8] Flemming Pociot,[9,10] Maria J. Redondo,[11] Stephen S. Rich,[12] Sarah J. Richardson,[13] Michael R. Rickels,[14] and R. David Leslie[15]

Diabetologia, Diabetes, Diabetes Care 2025



easd.org

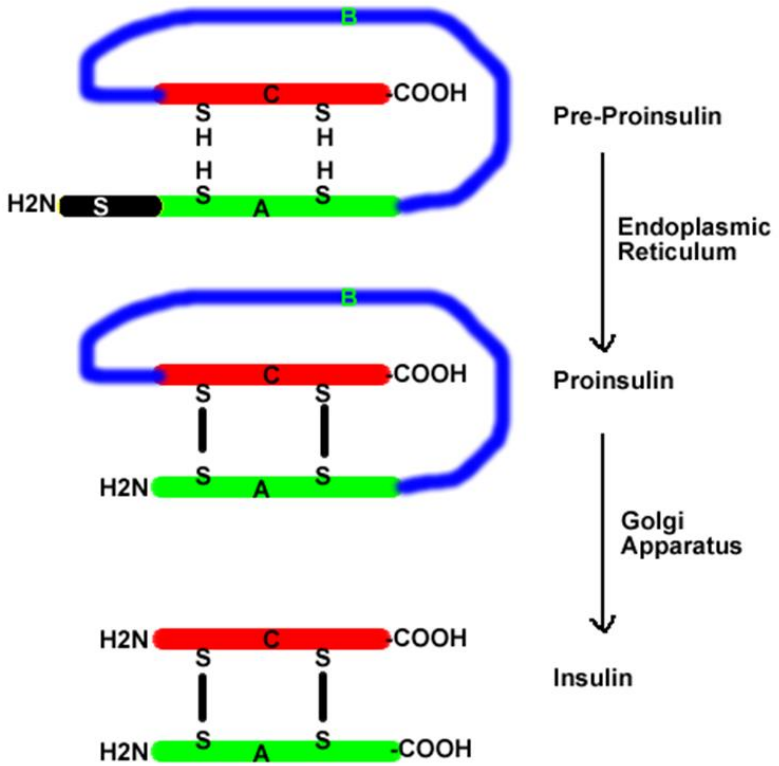
T1D: Time for change

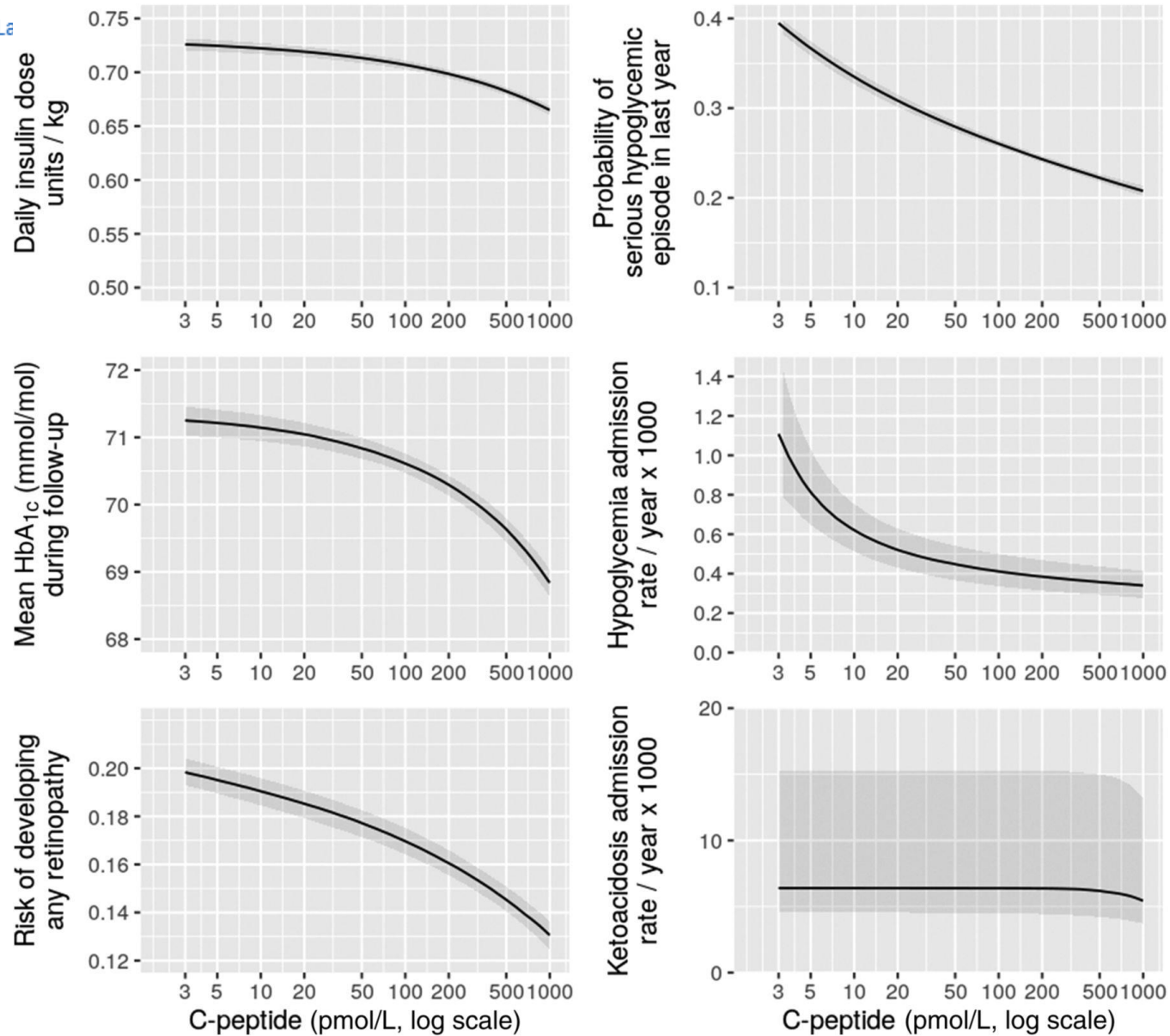


Sims EK, et. al. Diabetes 2022;71:610–3; Besser RE, et al. Pediatr Diabetes 2022;23:1175–87

Evidence for C-Peptide as a Validated Surrogate to Predict Clinical Benefits in Trials of Disease-Modifying Therapies for Type 1 Diabetes FREE

Esther Latres; Carla J. Greenbaum; Maria L. Oyaski; Colin M. Dayan; Helen M. Colhoun; John M. La
Jay S. Skyler; Michael R. Rickels; Simi T. Ahmed; Sanjoy Dutta; Kevan C. Herold; Marjana Marinac





Latres E et al Diabetes 2024;73(6):823–833

Precision Prognosis

age

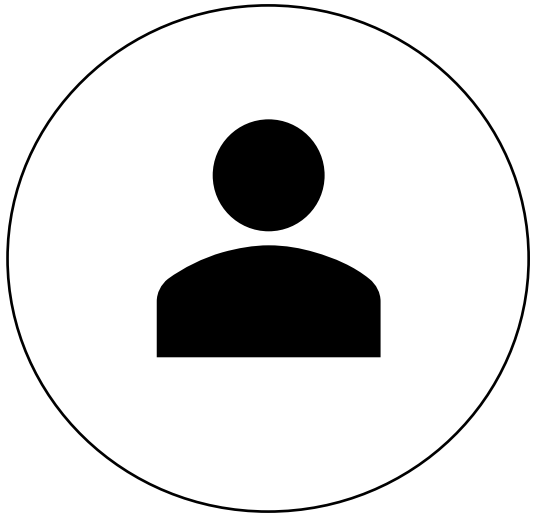
weight

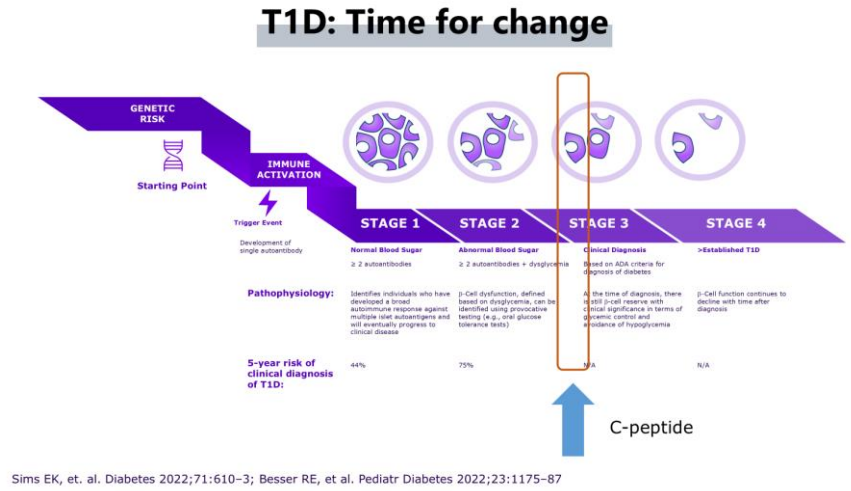
blood pressure

lipid profile

medication use

HbA1c





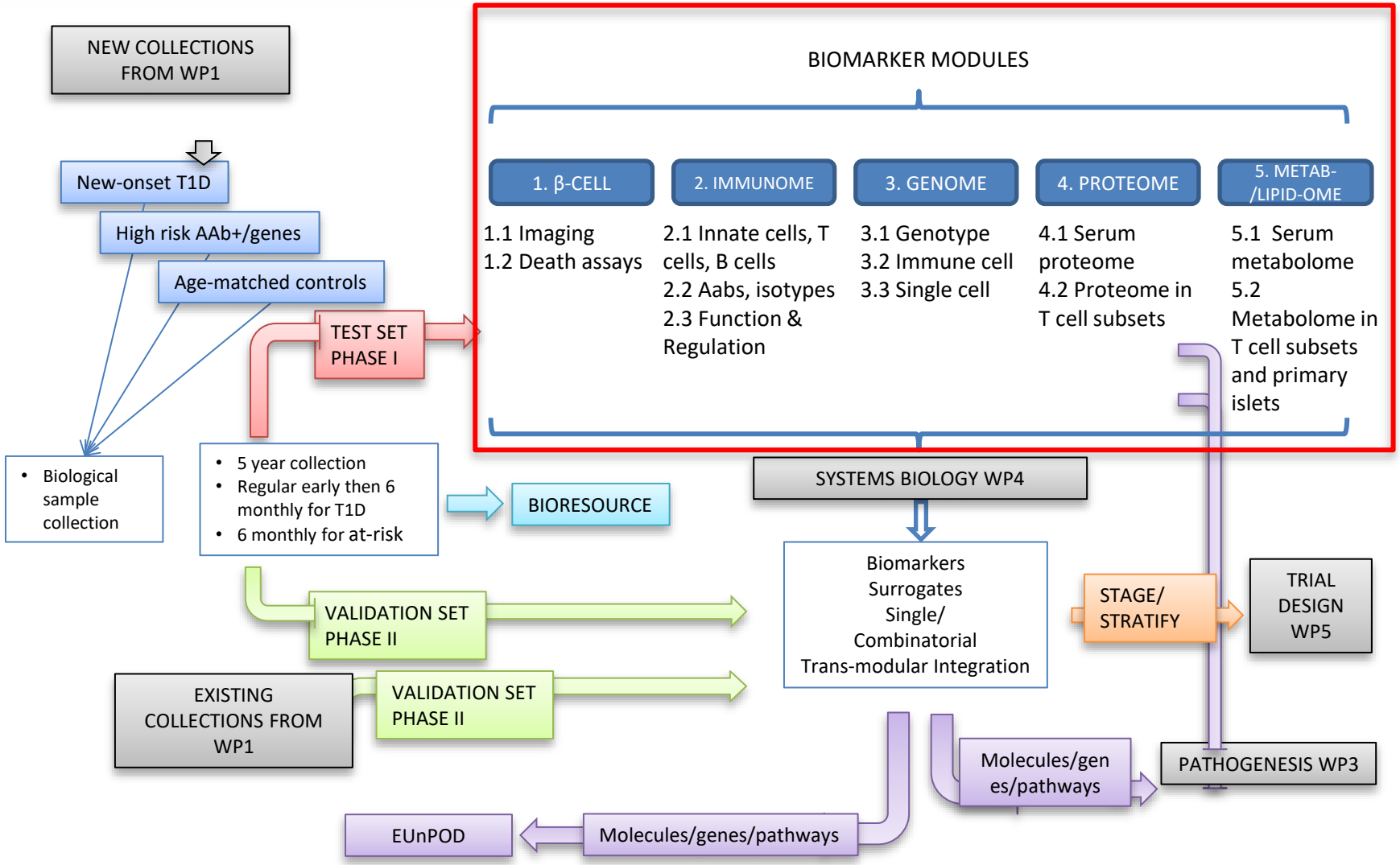
Sims EK, et. al. Diabetes 2022;71:610–3; Besser RE, et al. Pediatr Diabetes 2022;23:1175–87

Novel biomarkers

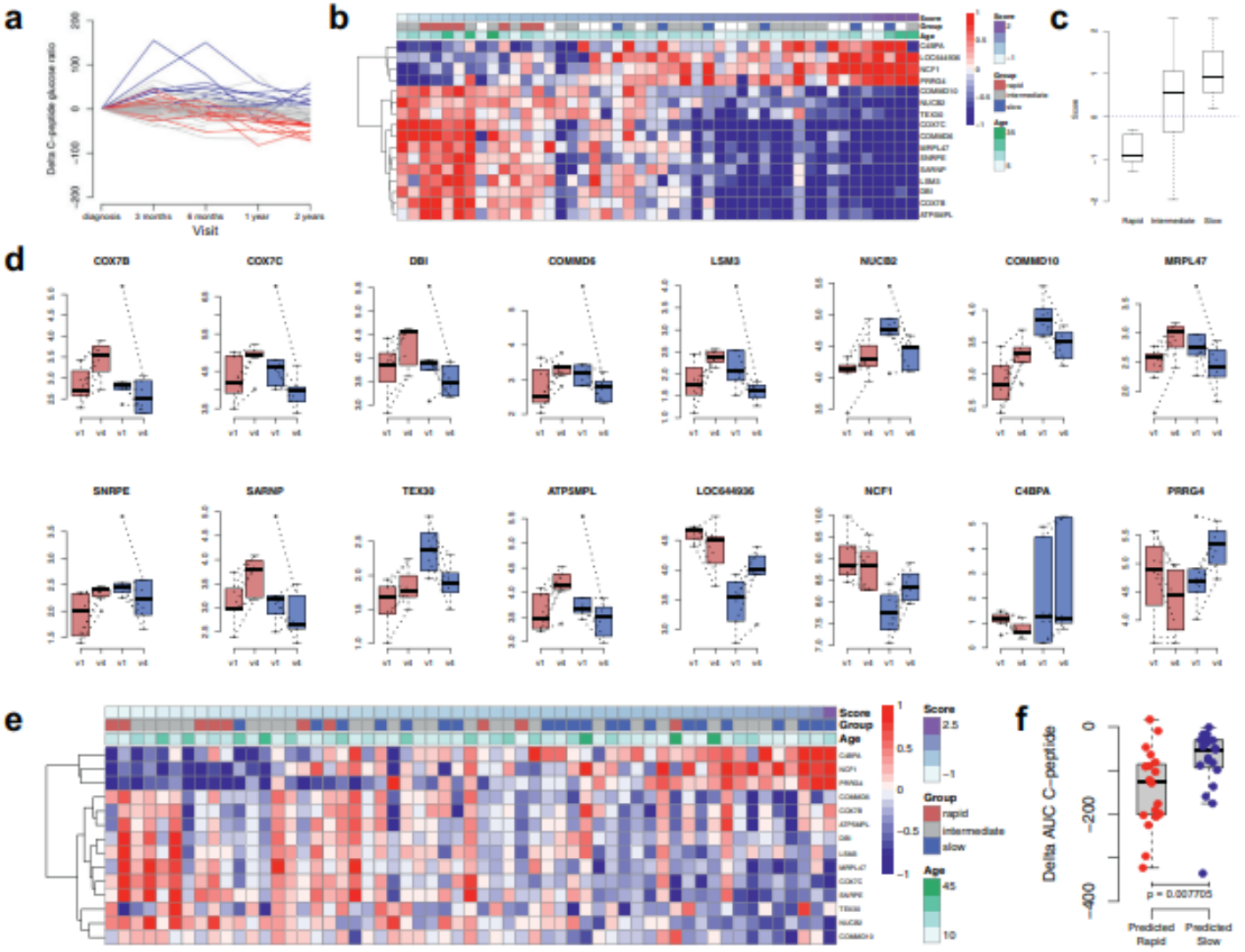
Arresting type 1 diabetes in Europe – biomarker discovery feeding interventions

www.INNODIA.eu; www.INNODIA.org

Biomarker discovery flow

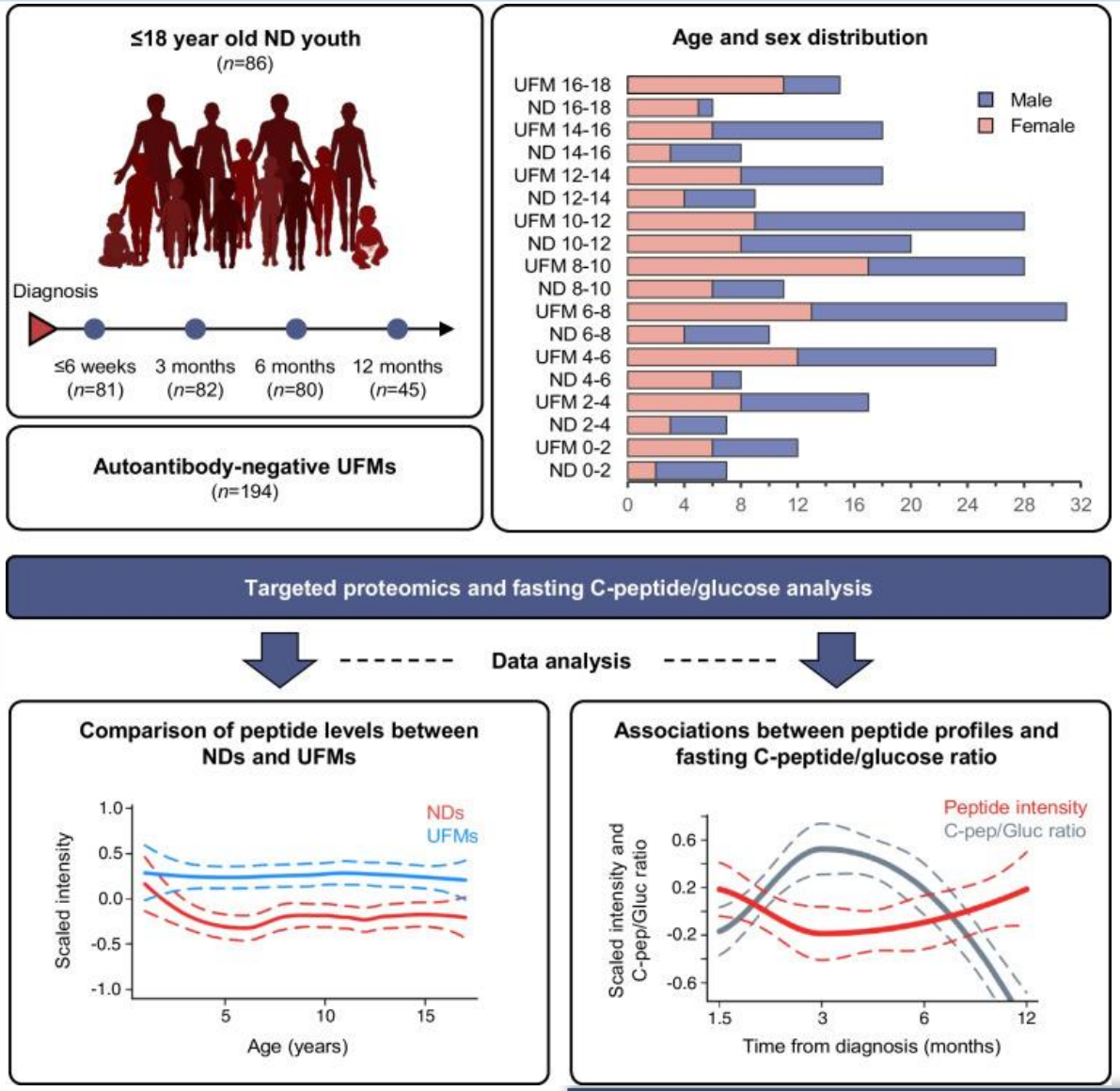


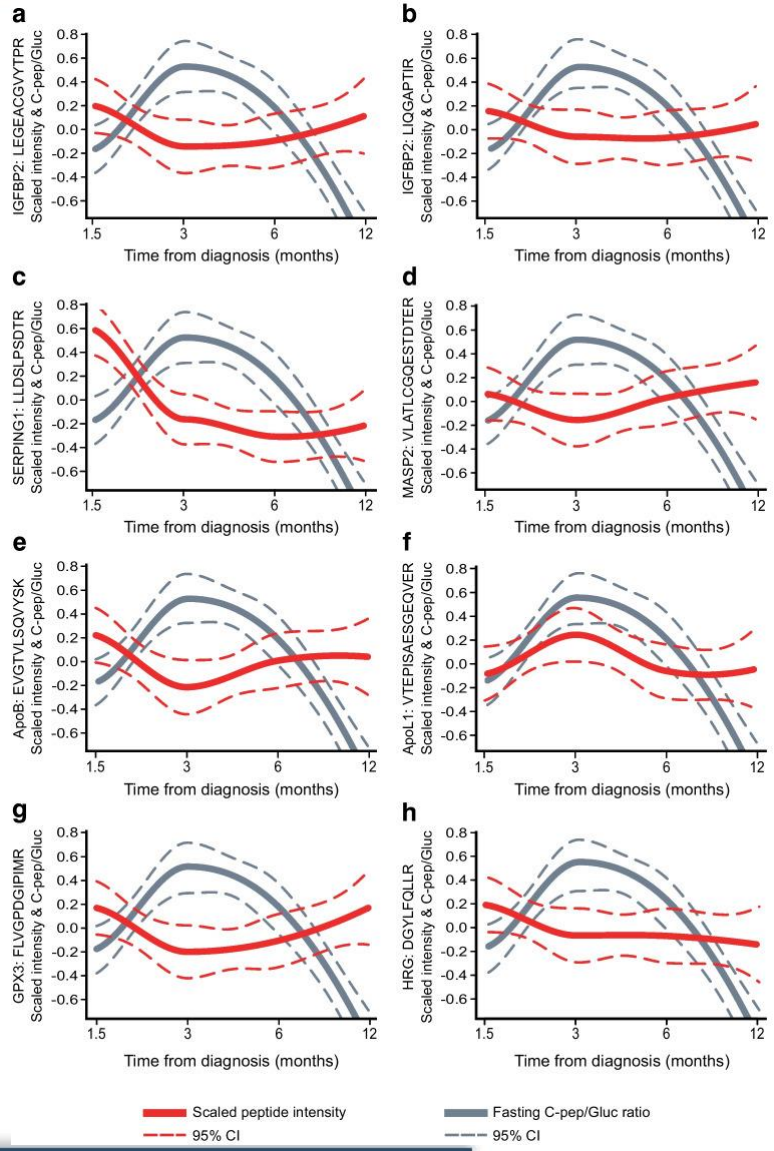
Gene expression signature predict speed of progression of C-peptide loss



Suomi T et al 2023 EBIOMedicine

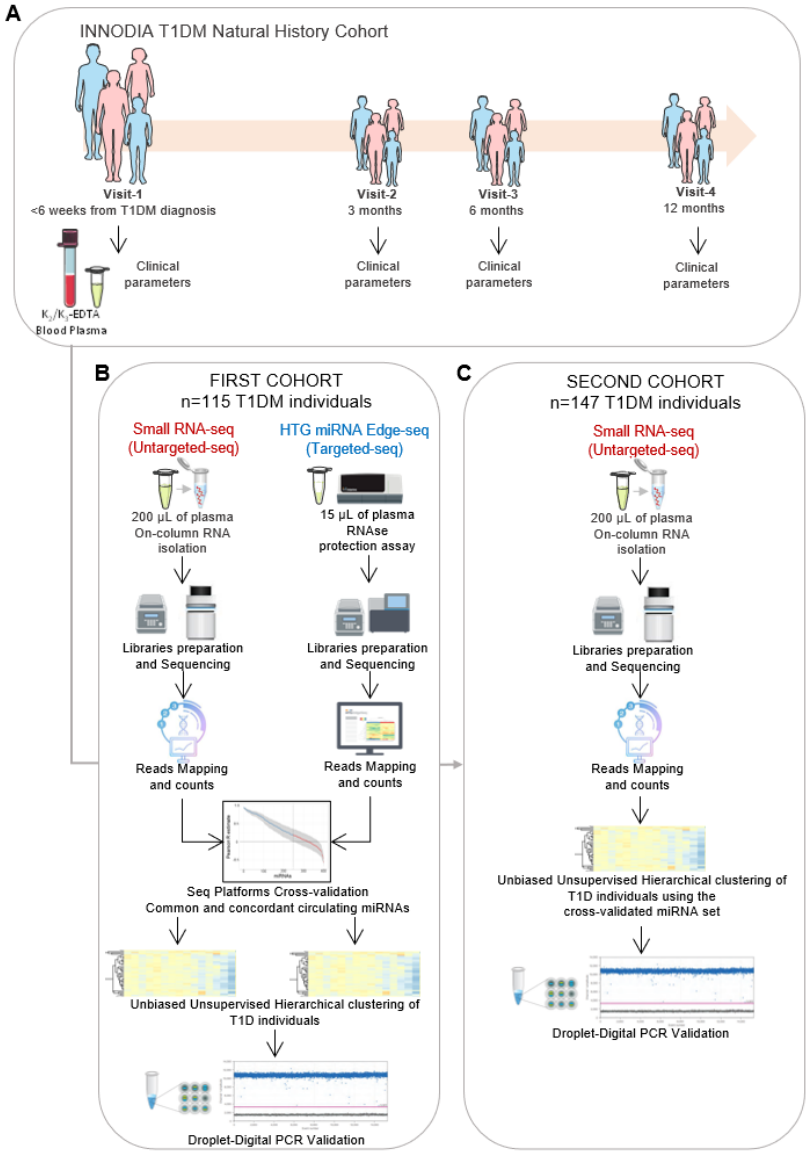
Proteome signature predict speed of progression of C-peptide loss





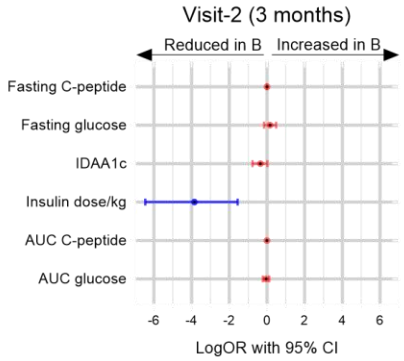
Moulder R et al 2023 Diabetologia

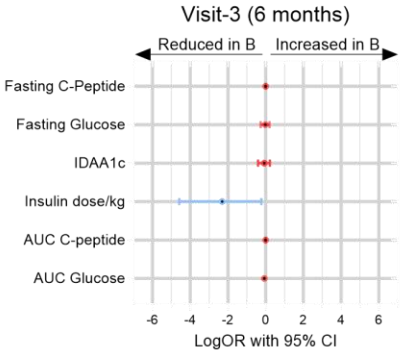
miRNA signatures predict speed of progression of C-peptide loss

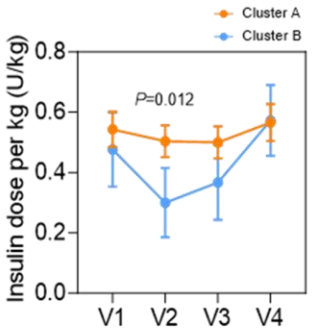


Circulating MicroRNAs

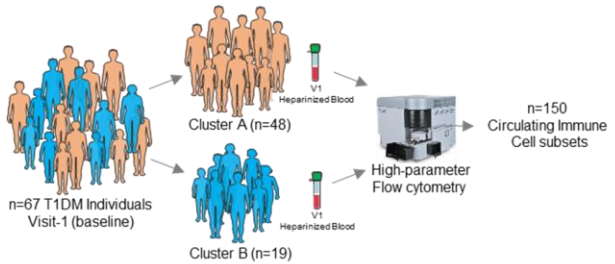
Clinical Parameters







Immunomics



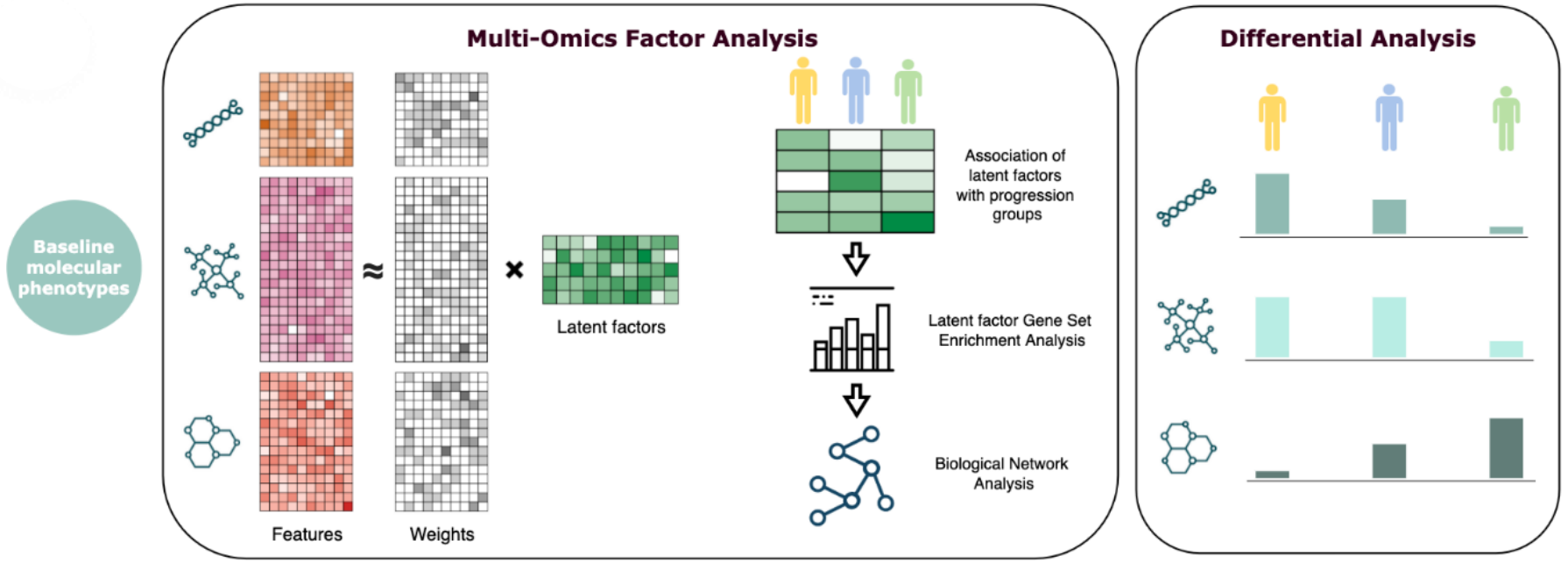
Immune cell subset	FC [B vs A]	P value	Padj
CD8+ Tscm	1,61	0,002	0,081
Th1-Th2-like Tfh	1,50	0,00008	0,012
TIGIT+ KLRG1- CD8+ Tem	1,26	0,002	0,081
TIGIT+ Tconv Tcm	1,12	0,002	0,081

Sebastiani G. et al., 2024, Cell Reports Medicine

Multi-Omics Integration

Multi-Omics data

- Transcriptomics
- miRNA (targeted and untargeted)
- Proteomics
- Lipidomics
- Metabolomics
- Immunomics



Objective

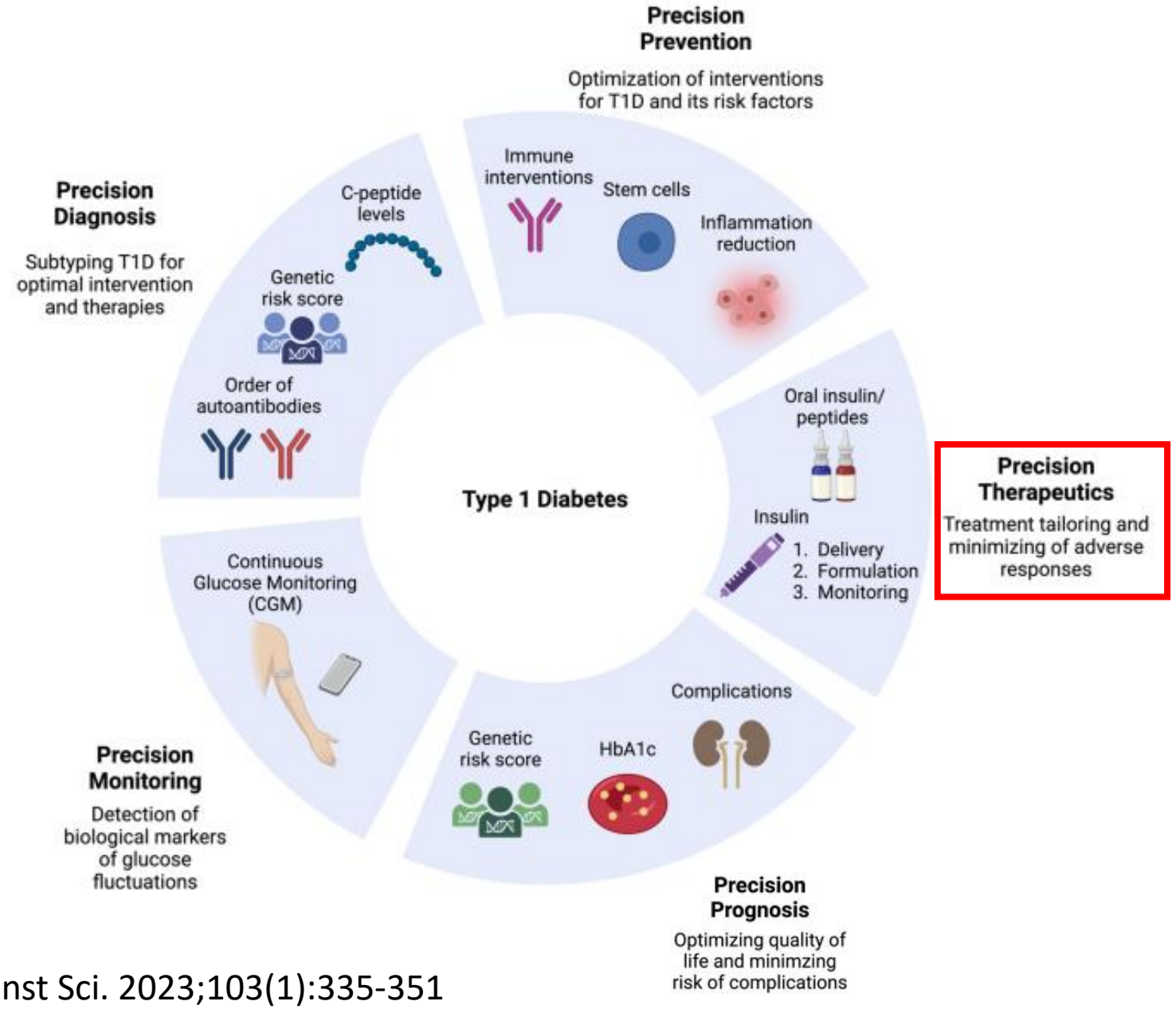
Integration of multi-omics dataset and association with disease progression groups

Methods

Multi-Omics Factor Analysis (MOFA) and differential analysis

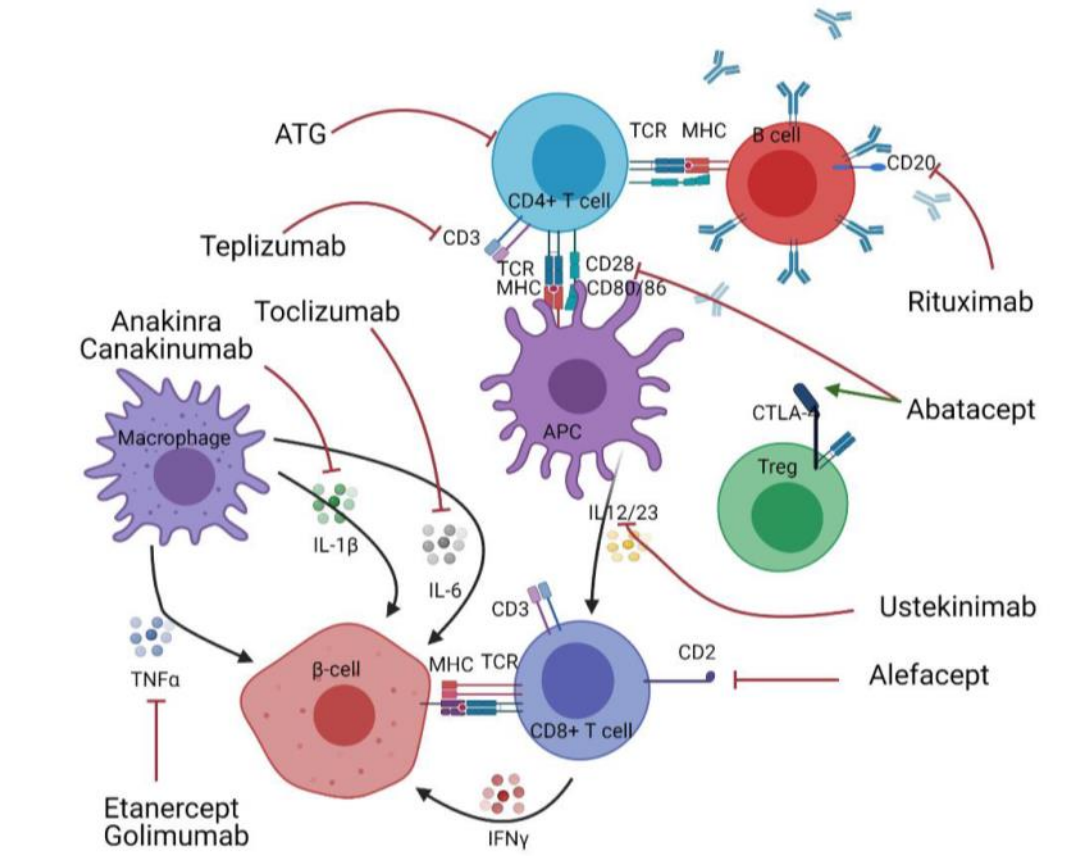
S. Brunak, Diab Res Clin pract 2024

Different aspects of precision medicine



Michalek DA et al J Indian Inst Sci. 2023;103(1):335-351

Disease modifying therapies in T1D



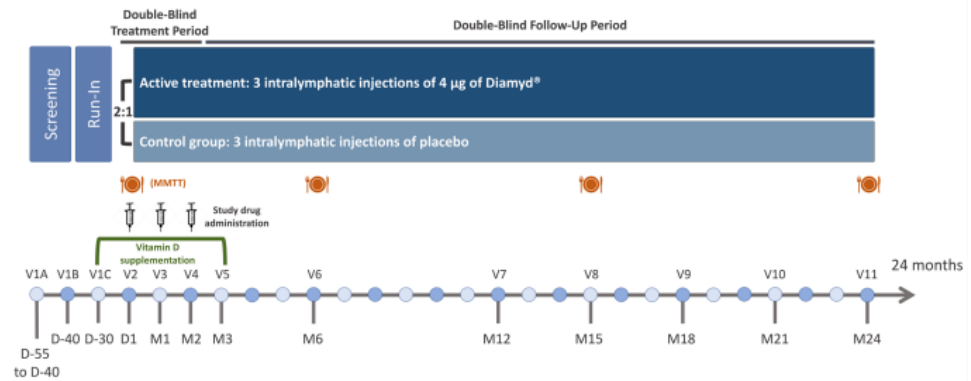
Intervention strategy	Preferred patient subgroup	Comment
Oral insulin	Patients with high IAA titers	Confirmed in replication trial.
Diamyd (GAD65)	GADA positive patients	GADA negative have not been assessed.
	Patients carrying HLA-DR3?	Suggested by *post-hoc* analyses of multiple trials.
Tolerance induction with proinsulin peptide	Patients carrying HLA-DR4	Proinsulin peptide C19-A3 was eluded from HLA-DR4 molecules.
Abatacept	Adolescents	Replication warranted.
	European ancestry?	Disease acceleration in patients of color.
Rituximab	Young patients	No efficacy achieved in adult patients; replication required. B-cells only present in insulitis in early onset T1D.
Islet transplantation	Patients lacking prior islet donor specific alloantibodies	A positive crossmatch consistently resulted acute allograft rejection.
	Patients lacking CD4 T-cell autoreactivity to GAD65 and IA2	None of patients responding to both GAD65 and IA-2 achieved insulin dependency, vs. >80% of patients not responding to either islet autoantigen; replicated in multiple studies.
	HLA class I mismatch avoids recurrent islet autoimmunity by CD8 T-cells	Indirect recognition of islet epitopes by recipients' HLA class II cannot still occur.
	Patients lacking pre-existent thyroid peroxidase (TPO) autoantibodies	All patients with TPO antibodies developed Graves' disease following discontinuation of immune suppression after graft failure vs. none of the TPO-negative recipients.
Autologous hematopoietic stem cell transplantation	Patients with low rates of CD8 T-cell autoimmunity to islets	Patients with CD8 islet autoimmunity in the lower 50th percentile all reached complete disease remission at least up to 900 days after therapy at which time 85% of patients with high islet autoimmunity had relapsed.
Fecal microbiome transplantation	Autologous stool preferred over allogeneic stool?	Disease progression only halted in patients receiving their own stool; patients had not been randomized according to composition of microbiome or rate of islet autoimmunity. p.m.: Autologous microbiota have recolonization advantage.

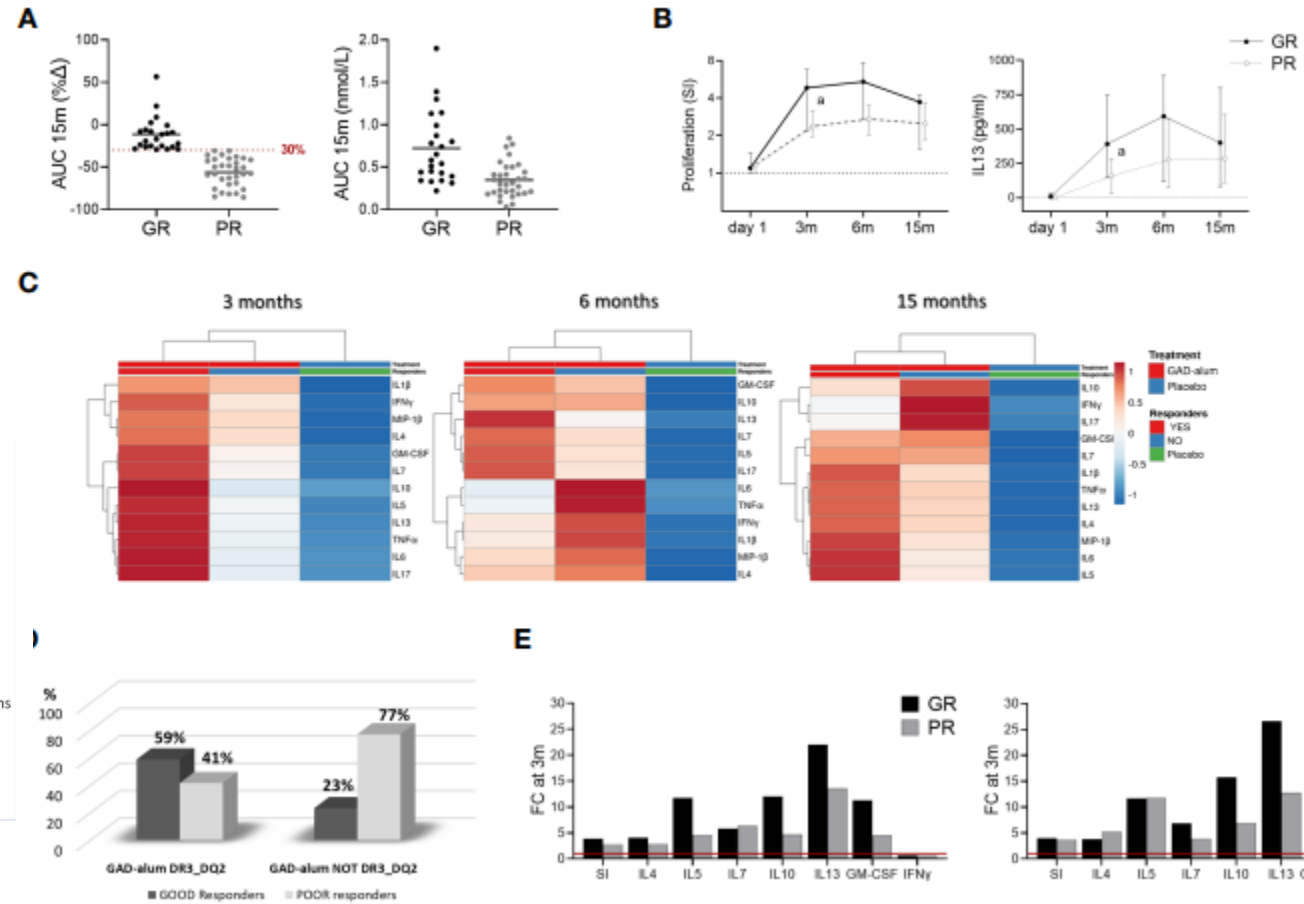
Pociot and Johannesen, Textbook of Diabetes (6th Edt)

Den Hollander NHM and BO Roep Front Med 2022 9:932086

Intralymphatic glutamic acid decarboxylase administration in type 1 diabetes patients induced a distinctive early immune response in patients with DR3DQ2 haplotype

Sara Puente-Marin[1], Fabrícia Dietrich[1], Peter Achenbach[2,3], Hugo Barcenilla[1], Johnny Ludvigsson[1,4] and Rosaura Casas[1]*



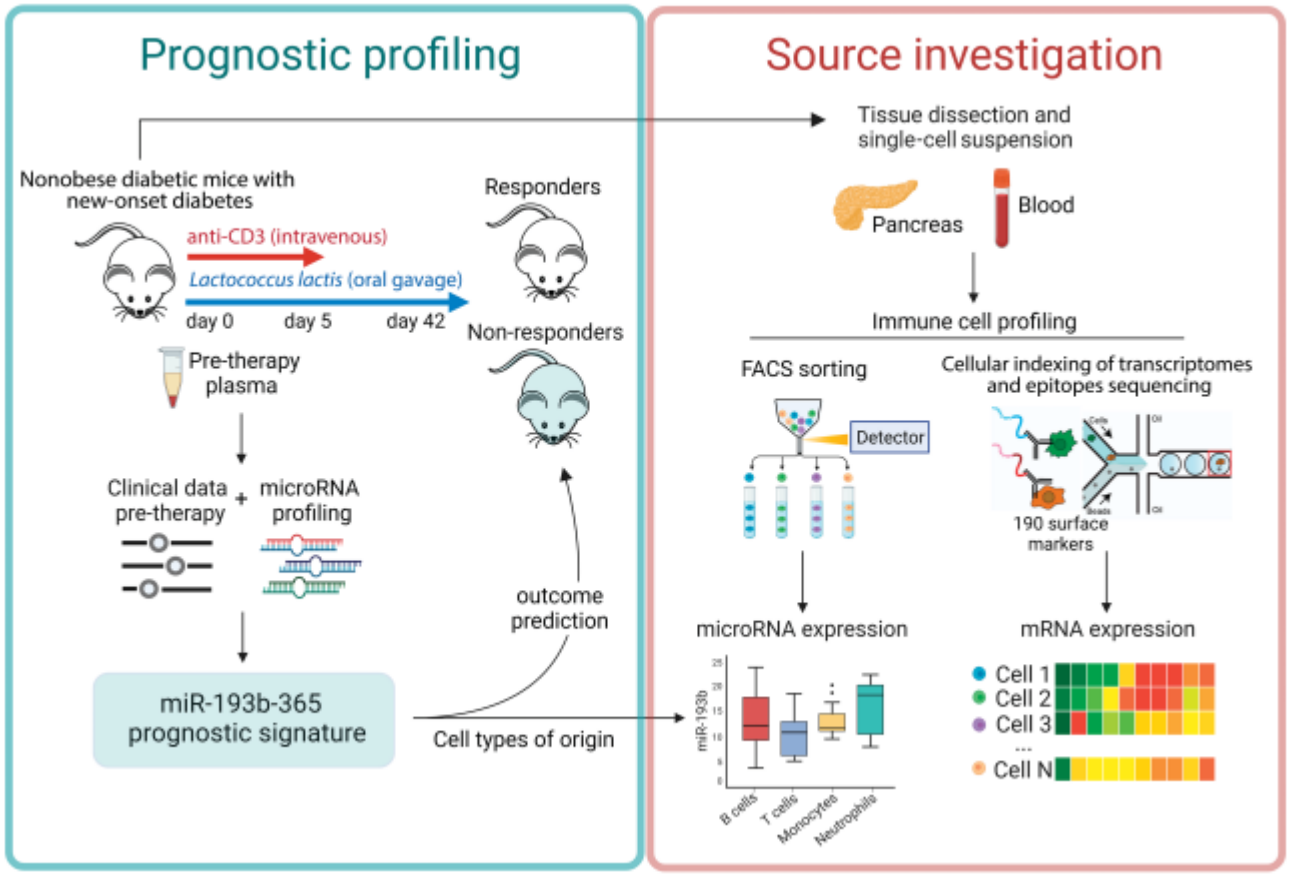


Ludvigsson J et al BMJ Open 2022;12:e061776; Puente-Marin S et al Front. Immunol. 2023 14:1112570

diabetes
American Diabetes Association

A Plasma miR-193b-365 Signature Combined With Age and Glycemic Status Predicts Response to *Lactococcus lactis*–Based Antigen-Specific Immunotherapy in New-Onset Type 1 Diabetes

Gabriele Sassi, Giada Licata, Giuliana Ventriglia, Amber Wouters, Pierre Lemaitre, Ruth Seurinck, Alessia Mori, Giuseppina Emanuela Grieco, Samal Bissenova, Darcy Ellis, Silvia Caluwaerts, Pieter Rottiers, Niels Vandamme, Chantal Mathieu, Francesco Dotta, Conny Gysemans, and Guido Sebastiani

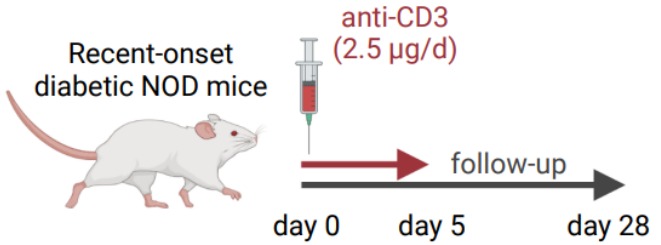


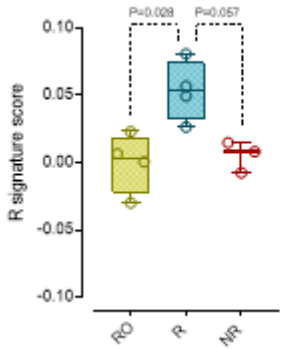
Sassi G et al Diabetes 2023;72(10):1470–1482

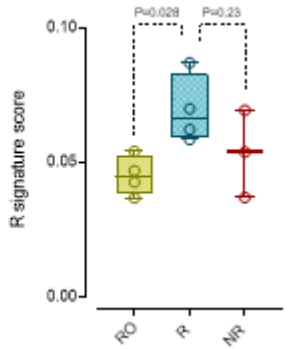
JCI The Journal of Clinical Investigation

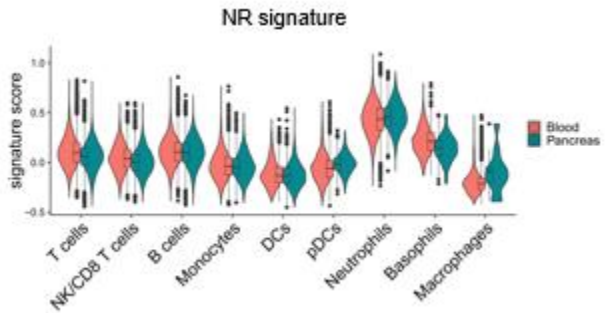
Signature of non-response to anti-CD3 therapy in NOD mice and people with Stage 2 and stage 3 T1D treated with teplizumab

Sassi G, Lemaitre P…Mathieu C, Gysemans C
2025 In Press

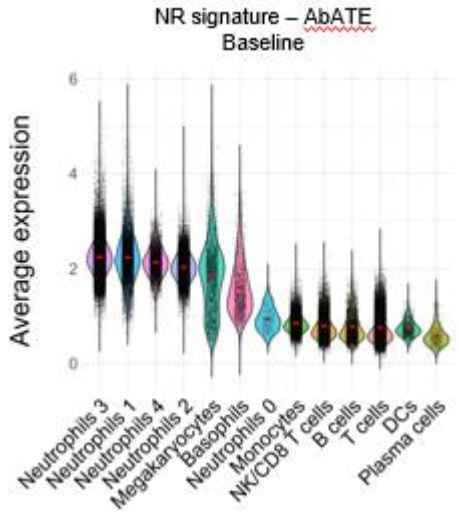




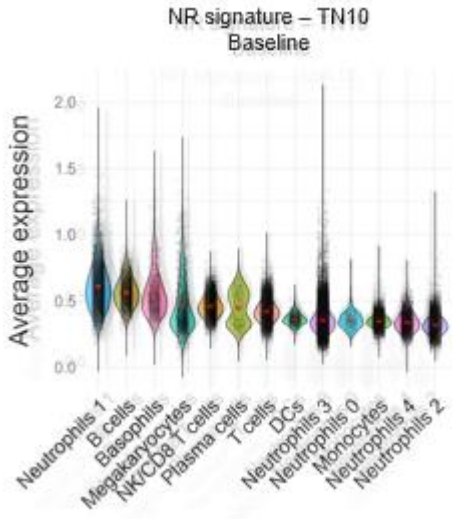




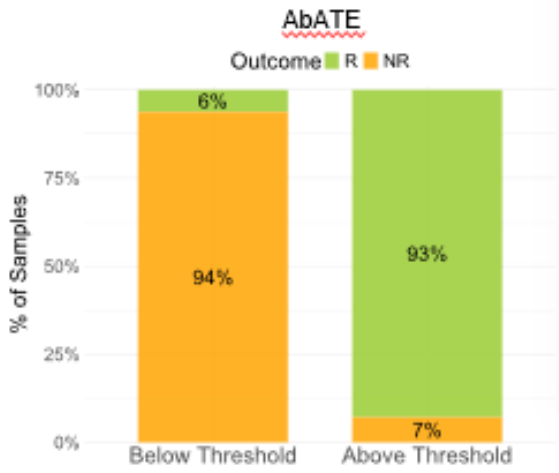
Stage 3

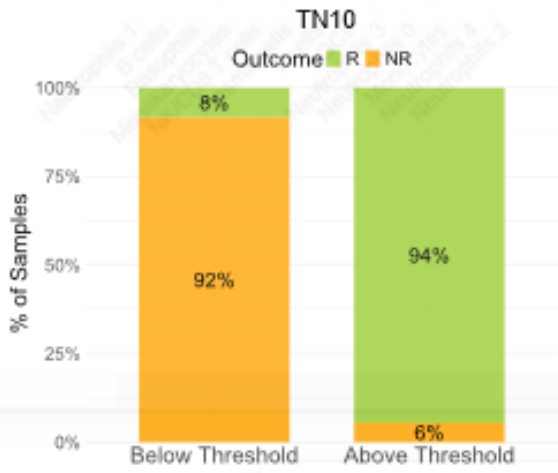


Stage 2

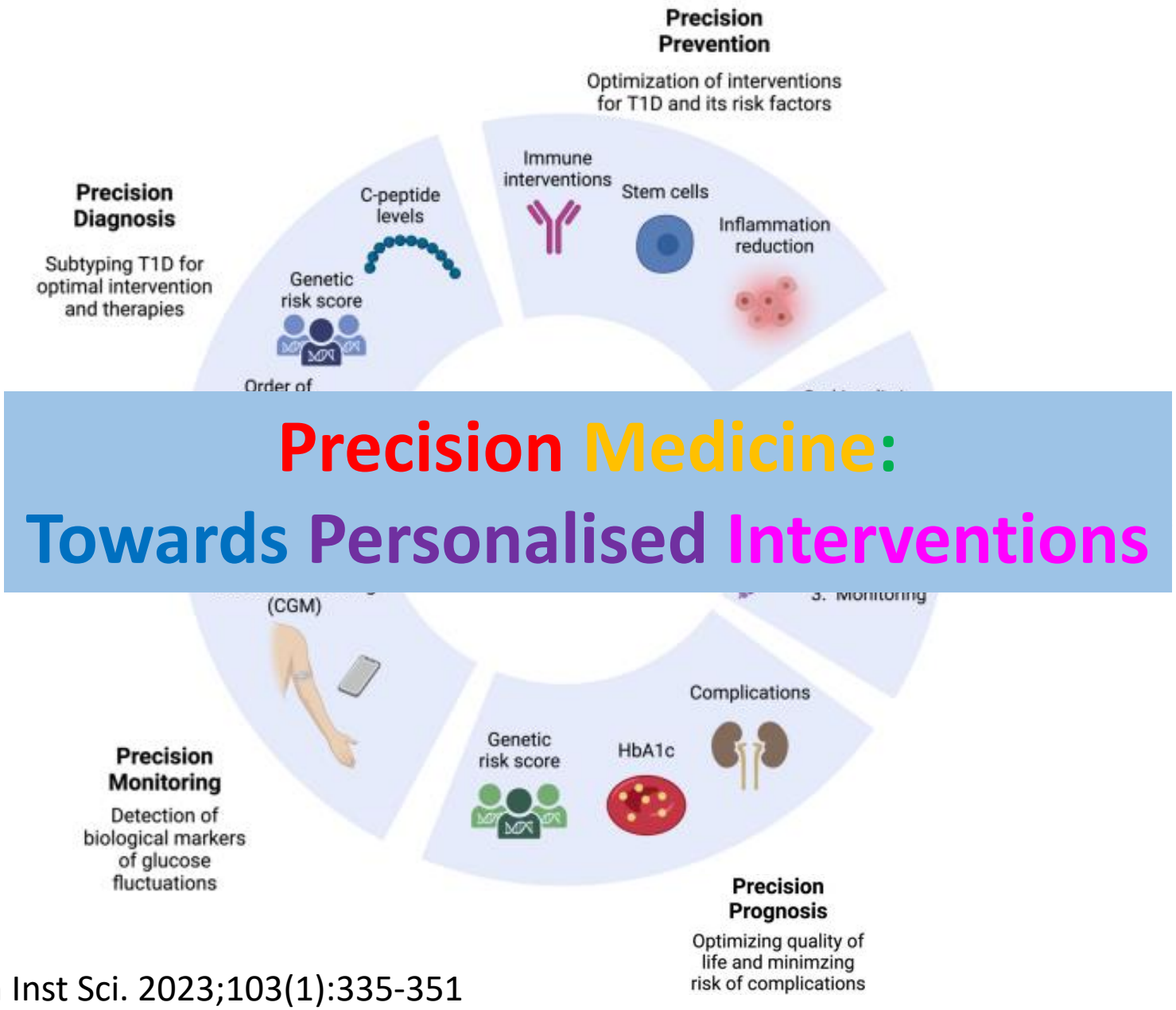


Baseline predictive response score associated with clinical response to teplizumab outcome in stage 2 and 3 type 1 diabetes





Precision medicine is changing the paradigm in T1D



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