Backgrounder

Type 2 Diabetes Subgroup Analysis

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Integrating data from Recent Findings (21st century):

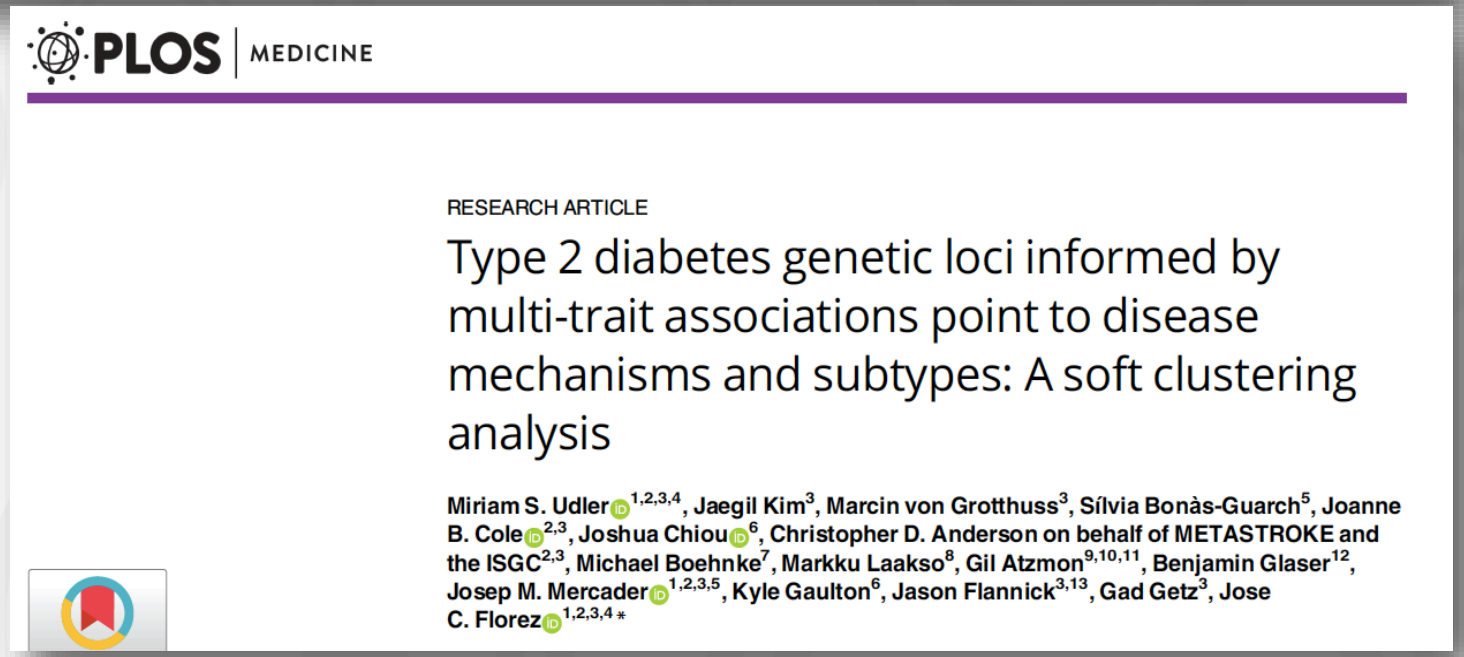
Revisiting the definition (and classification) of T2D

Ahlquist

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki*, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop

Udler



PLOS MEDICINE

RESEARCH ARTICLE

Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis

Miriam S. Udler[1,2,3,4], Jaegil Kim[3], Marcin von Grotthuss[3], Sílvia Bonàs-Guarch[5], Joanne B. Cole[2,3], Joshua Chiou[6], Christopher D. Anderson on behalf of METASTROKE and the ISGC[2,3], Michael Boehnke[7], Markku Laakso[8], Gil Atzmon[9,10,11], Benjamin Glaser[12], Josep M. Mercader[1,2,3,5], Kyle Gaulton[6], Jason Flannick[3,13], Gad Getz[3], Jose C. Florez[1,2,3,4]*

ARTICLES
https://doi.org/10.1038/s41588-021-00948-2
nature genetics

Genome-wide association analyses highlight etiological differences underlying newly defined subtypes of diabetes

Dina Mansour Aly[1], Om Prakash Dwivedi[2], Rashmi B. Prasad[1], Annemari Käräjämäki[3,4], Rebecka Hjort[5], Manonanthini Thangam[1], Mikael Åkerlund[1], Anubha Mahajan[6,16], Miriam S. Udler[7,8,9], Jose C. Florez[7,8,9], Mark I. McCarthy[10,11,12,16], Regeneron Genetics Center*, Julia Brosnan[13,18], Olle Melander[1], Sofia Carlsson[5], Ola Hansson[1,2], Tiinamaija Tuomi[1,2,14,15], Leif Groop[1,2] and Emma Ahlqvist[1]✉

Diabetologia (2022) 65:206–215
https://doi.org/10.1007/s00125-021-05567-4

ARTICLE

Validation of the classification for type 2 diabetes into five subgroups: a report from the ORIGIN trial

Marie Pigeyre[1,2,3] · Sibylle Hess[4] · Maria F. Gomez[5] · Olof Asplund[6,7] · Leif Groop[6,7] · Guillaume Paré[1,2,8,9] · Hertzel Gerstein[1,2,3,9]

Received: 9 March 2021 / Accepted: 14 July 2021 / Published online: 21 October 2021

REVIEW ARTICLE

New and Unique Clusters of Type 2 Diabetes Identified in Indians

Ranjit Mohan Anjana[1], Rajendra Pradeepa[1], Ranjit Unnikrishnan[1], Mangesh Tiwaskar[2], Sosale R Aravind[3], Banshi Saboo[4], Shashank R Joshi[5], Viswanathan Mohan[1*]

Diabetes Subgroup Clustering Provide Validated Biomarkers

Pre-Diabetes

Initial Decline in Glycemic Control
Increasing HbA1c, Increasing Insulin Resistance
Decreasing beta cell numbers and function

T2D

HbA1c
HOMA-B
HOMA-IR
BMI
Age

18%

SIDD = Severe Insulin Deficient Diabetes
Low insulin secretion, poor metabolic control, increased risk of retinopathy and neuropathy

15%

SIRD = Severe Insulin Resistant Diabetes
Insulin resistance, obesity, late onset, increased risk of nephropathy and fatty liver

22%

MOD = Mild Obesity-Related Diabetes
Obesity, early onset

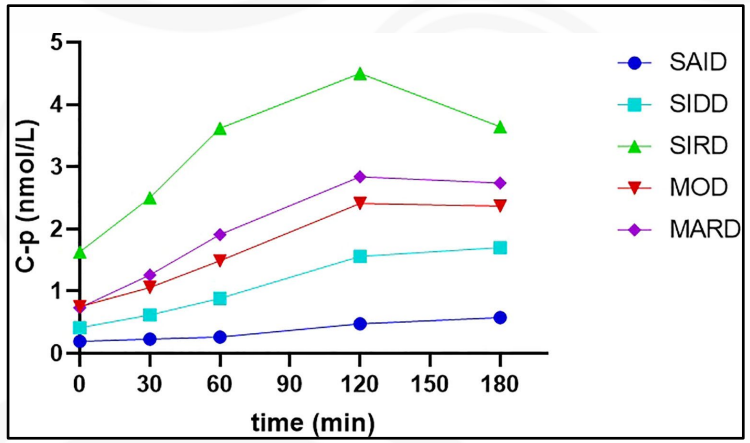
39%

MARD = Mild Age-Related Diabetes
Late onset, low risk of complications

T1D

Initial Diagnosis/Disease – Stage 2/Stage 3
Increasing HbA1c, Initial Reduction in Insulin
Significant Decrease in beta cell numbers

Targeted Patient Population for BMF-219

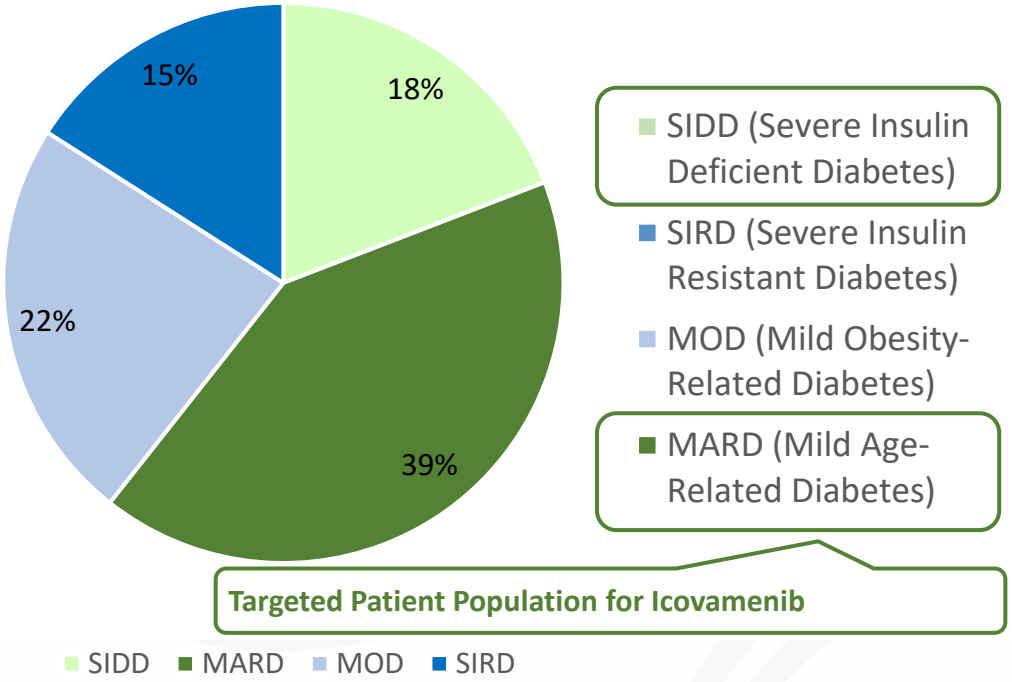


Adjusted from Ahlqvist et al. Diabetes 2020;69:2086–2093 | https://doi.org/10.2337/dbi20-0001

Song et al. Front Endocrinol (Lausanne). 2022 Jul 27:13:927661. doi: 10.3389/fendo.2022.927661. eCollection 2022.

According to Diabetes Subgroup Clusters, 50%-60% T2D Patients are Beta-Cell/Insulin Deficient (– Potential Population that Benefits the Most from Icovamenib)

T2D Patient Distribution based on US Population



	Patient Distribution (%)	Age (years), Median	HbA1c (mmol/mol) Median	BMI (kg/m^2) Median	HOMA2-B (%) Median	HOMA2-IR (%) Median
SIDD	18%	55 (48-61)	67 (64-74)	29 (27-32)	49 (38-59)	2.3 (1.8-2.8)
MARD	39%	61 (55-66)	53 (49-56)	29 (26-31)	64 (53-76)	2.3 (1.8-2.7)
MOD	22%	47 (41-52)	55 (51-61)	36 (33-40)	74 (59-89)	3.1 (2.4-3.7)
SIRD	15%	59 (53-66)	53 (48-60)	34 (30-38)	101 (87-121)	4.0 (3.4-4.7)

*SIDD and MARD are characterized by low BMI, low beta-cell function/insulin production, and low insulin resistance.

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Adjusted from Dennis et al. Lancet Diabetes Endocrinol. 2019 Jun; 7(6): 442–451; Zou et al. Lancet Diabetes Endocrinol. 7(1), 9–11 (2019)

DDZ Diabetes Cluster Identification Online Tool

German Diabetes Center

Input: Age at diagnosis, BMF, fasting plasma glucose, fasting C-Peptide, HbA1c, sex

Input

DDZ Diabetes-Cluster-Tool

Deutsch (https://diabetescalculator.ddz.de/diabetescluster)

GAD-Antibodies

Not Present

Note: When GAD-Antibodies are present the person is automatically assigned to the subtype 1/SAID.

Age at diagnosis (years)

55

BMI (kg/m²)

26.9

Plasma glucose unit (mmol/l or mg/dl)

mg/dl

Fasting plasma glucose (fasting blood sugar)

227

C-Peptide unit (ng/ml, nmol/l or pmol/l)

ng/ml

Fasting C-Peptide

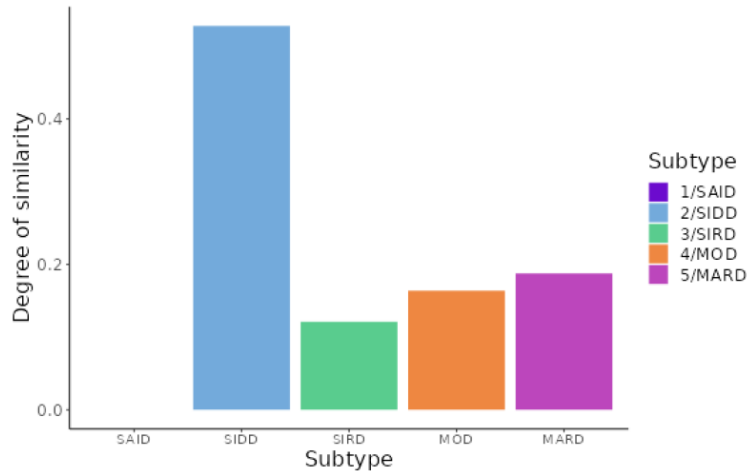
3.63

HbA1c (%)

10.1

This person most resembles the diabetes subtype:

2/SIDD



The **DDZ Diabetes-Cluster-Tool** assigns people with diabetes to one of the five diabetes subtypes (diabetes clusters). In addition, it graphically depicts the degree of similarity to each of the five subtypes.

The diabetes subtypes are:

- 1/SAID: Severe autoimmune diabetes
- 2/SIDD: Severe insulin-deficient diabetes
- 3/SIRD: Severe insulin-resistant diabetes
- 4/MOD: Mild obesity-related diabetes
- 5/MARD: Mild age-related diabetes

References

Ahlqvist, E., Storm, P., Käräjämäki, A., Martinell, M., Dorkhan, M., Carlsson, A., ... & Groop, L. (2018). Novel

DDZ Diabetes Cluster Tool [DDZ Diabetes-Cluster-Tool]

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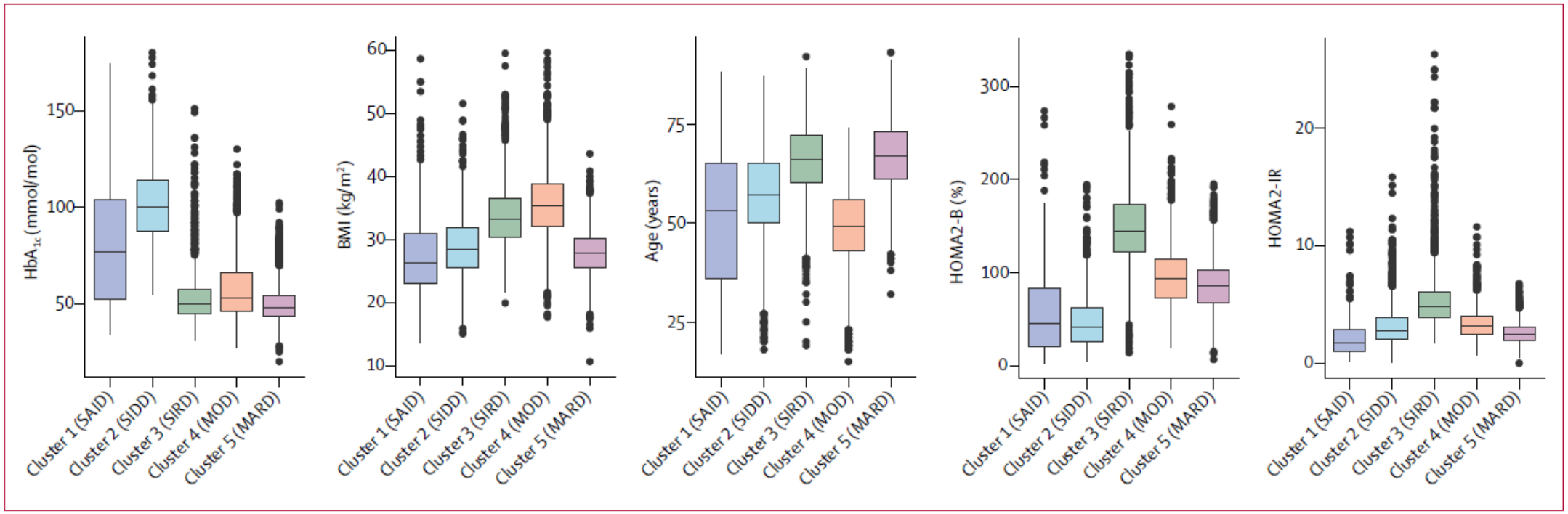
Five Reproducible Clusters leading to Precision Medicine in Diabetes



Cluster 1: Severe Autoimmune Diabetes (SAID)
Cluster 2: Severe Insulin-Deficient Diabetes (SIDD)
Cluster 3: Severe Insulin-Resistant Diabetes (SIRD)
Cluster 4: Mild Obesity Diabetes (MOD)
Cluster 5: Mild Age-Related Diabetes (MARD)

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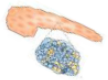
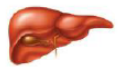
Ahlquist et al. Lancet Diabetes Endocrinol 2018; 6: 361–69

Key Trait & Variant Associations for the 5 Subgroup Clusters

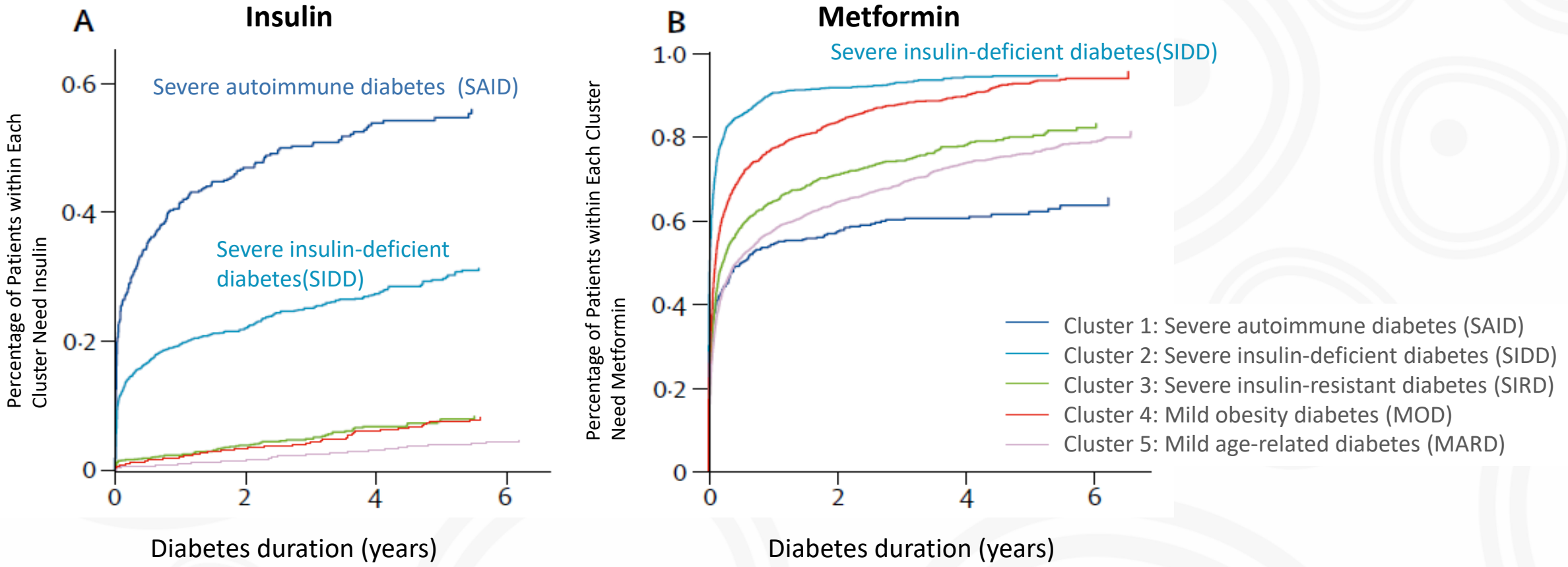
	Cluster name	Key traits	Key genetic loci	Suspected mechanism
Insulin Deficiency	 Beta Cell	↓ **Fasting insulin**, Insulin response to glucose stimulation ↑ **Proinsulin**	*MTNR1B, HHEX, TCF7L2, SLC30A8, HNF1A, HNF1B*	**Insulin processing/ secretion**
Insulin Deficiency	 Proinsulin	↓ **Fasting insulin,** Insulin response to glucose stim ↓ **Proinsulin**	*ARAP1, SPRY2, DGKB*	**Insulin synthesis**
Insulin Resistance	 Obesity	↑ **Fasting insulin** ↑ **BMI, %Body Fat,** Waist Circ, Hip Circ	*FTO, MC4R, NRXN3*	**Obesity-mediated IR**
Insulin Resistance	 Lipodystrophy	↑ **Fasting insulin** ↓ **BMI, %Body Fat,** HDL	*IRS1, GRB14, PPARG, LYPLAL1, ANKRD55*	**Fat distribution- mediated IR**
Insulin Resistance	 Liver/Lipid	↑ **Fasting insulin** ↓ **Triglycerides,** palmitoleic acid, linolenic acid	*GCKR, TM6SF2, HLA.DQA1, PNPLA3*	**Liver/lipid metabolism**

Udler et al. PLoS Med 2018 Sep 21;15(9):e1002654

Significant Number of Diabetes Patients Are Insulin-Dependent

~30% Severe Insulin-Deficient Diabetes Patients (SIID) are Insulin Dependent by Year 5 of Diagnosis

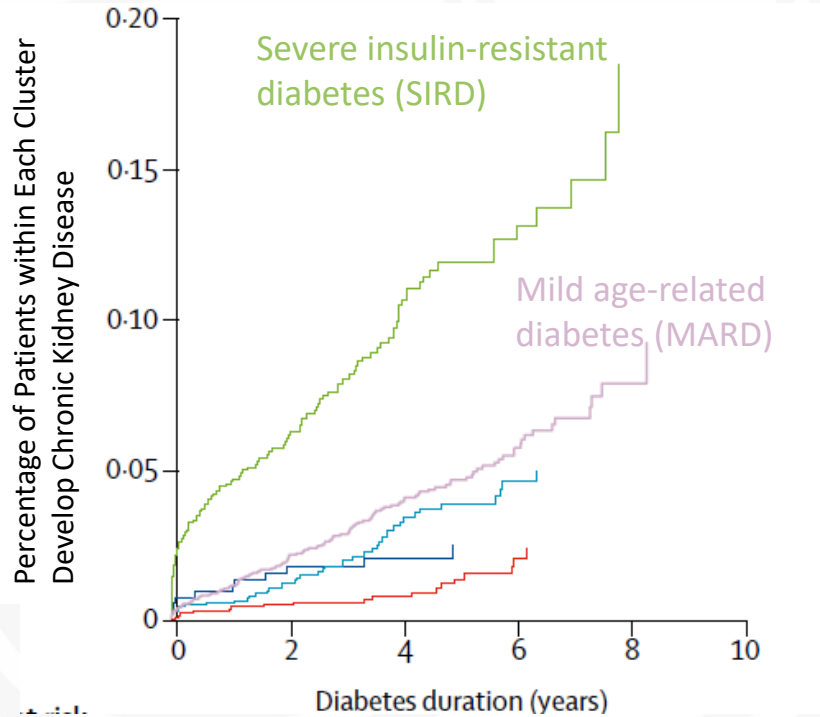
~90% of the Severe Insulin Deficient Diabetes Patients are Metformin Dependent by Year 2 of Diagnosis



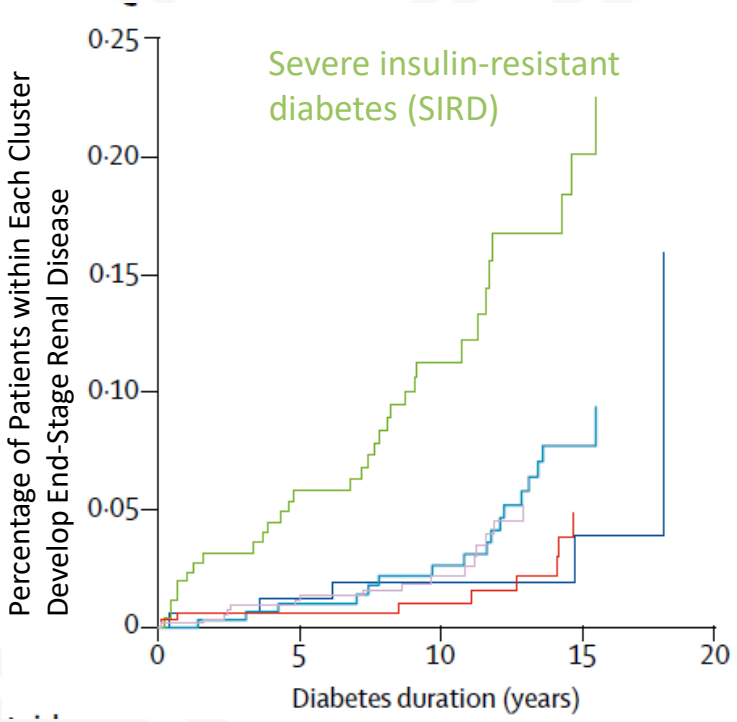
Ahlquist et al. Lancet Diabetes Endocrinol 2018; 6: 361–69

Diabetes Subgroup Clusters Provide a More Precise Clinically Useful Stratification towards Precision Medicine in Diabetes

Chronic Kidney Disease



End-Stage Renal Disease



Severe insulin-resistance diabetes patients have the highest risk of developing chronic kidney disease and end-stage renal disease.

- Cluster 1: Severe autoimmune diabetes (SAID)
- Cluster 2: Severe insulin-deficient diabetes (SIDD)
- Cluster 3: Severe insulin-resistant diabetes (SIRD)
- Cluster 4: Mild obesity diabetes (MOD)
- Cluster 5: Mild age-related diabetes (MARD)

Ahlquist et al. Lancet Diabetes Endocrinol 2018; 6: 361–69

Relevant Literature

Novel subgroups of adult-onset diabetes and there association with outcomes: a data-driven cluster analysis of six variables
Emma Ahlqvist et al. 2018 May;6(5):361-369. doi: 10.1016/S2213-8587(18)30051-2. Epub 2018 Mar 5.

Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data
John M Dennis, Beverley M Shields, William E Henley, Angus G Jones, Andrew T Hattersley. Lancet Diabetes Endocrinol 2019; 7: 442–51

Subtypes of Type 2 Diabetes Determined From Clinical Parameters
Emma Ahlqvist,1 Rashmi B. Prasad,1 and Leif Groop. Diabetes 2020;69:2086–2093 | https://doi.org/10.2337/dbi20-0001

Novel strategies for glycaemic control and preventing diabetic complications applying the clustering-based classification of adult-onset diabetes mellitus: A perspective
Hayato Tanabe, Hiroaki Masuzaki, Michio Shimabukuro. 2021 Oct:180:109067. doi: 10.1016/j.diabres.2021.109067. Epub 2021 Sep 23.

The Identification of Diabetes Mellitus Subtypes Applying Cluster Analysis Techniques: A Systematic Review
Antonio Sarría-Santamera, Binur Orazumbekova, Tilektes Maulenkul, Abduzhappar Gaipov and Kuralay Atageldiyeva
PMID:**33353219,** PMCID: PMC7766625, DOI: 10.3390/ijerph17249523

Etiologies underlying subtypes of longstanding type 2 diabetes
Riad Bayoumi*, et al., 2024 May 28;19(5):e0304036. doi: 10.1371/journal.pone.0304036. eCollection 2024.

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THANK YOU

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