Quando anche la diagnostica non è semplice: vecchie e nuove definizioni

Marco Giorgio Baroni

Dipartimento di Medicina Clinica, Sanità Pubblica, Scienze della Vita e dell'Ambiente (MeSVA)

Università dell'Aquila

Direttore UOC Andrologia Medica e Diabetologia

Ospedale S. Salvatore, ASL1 Abruzzo, L'Aquila

UNIVERSITÀ DEGLI STUDI DELL'AQUILA

MESVA

Conflitto di Interessi

Negli ultimi due anni Marco G. Baroni ha ricevuto compensi per relazioni e/o consulenze da:

- Lilly, Novo Nordisk, Boheringer, Abbot, MSD, Viatris

La struttura di apparteneza di MG Baroni ha ricevuto:

- Compensi per studi clinici sponsorizzati da: Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Quando anche la diagnostica non è semplice: vecchie e nuove definizioni

Agenda

- Verso una diagnosi di precisione del diabete
  - Basata su marcatori sempilci
  - Complessa

- Diabete tipo 3c

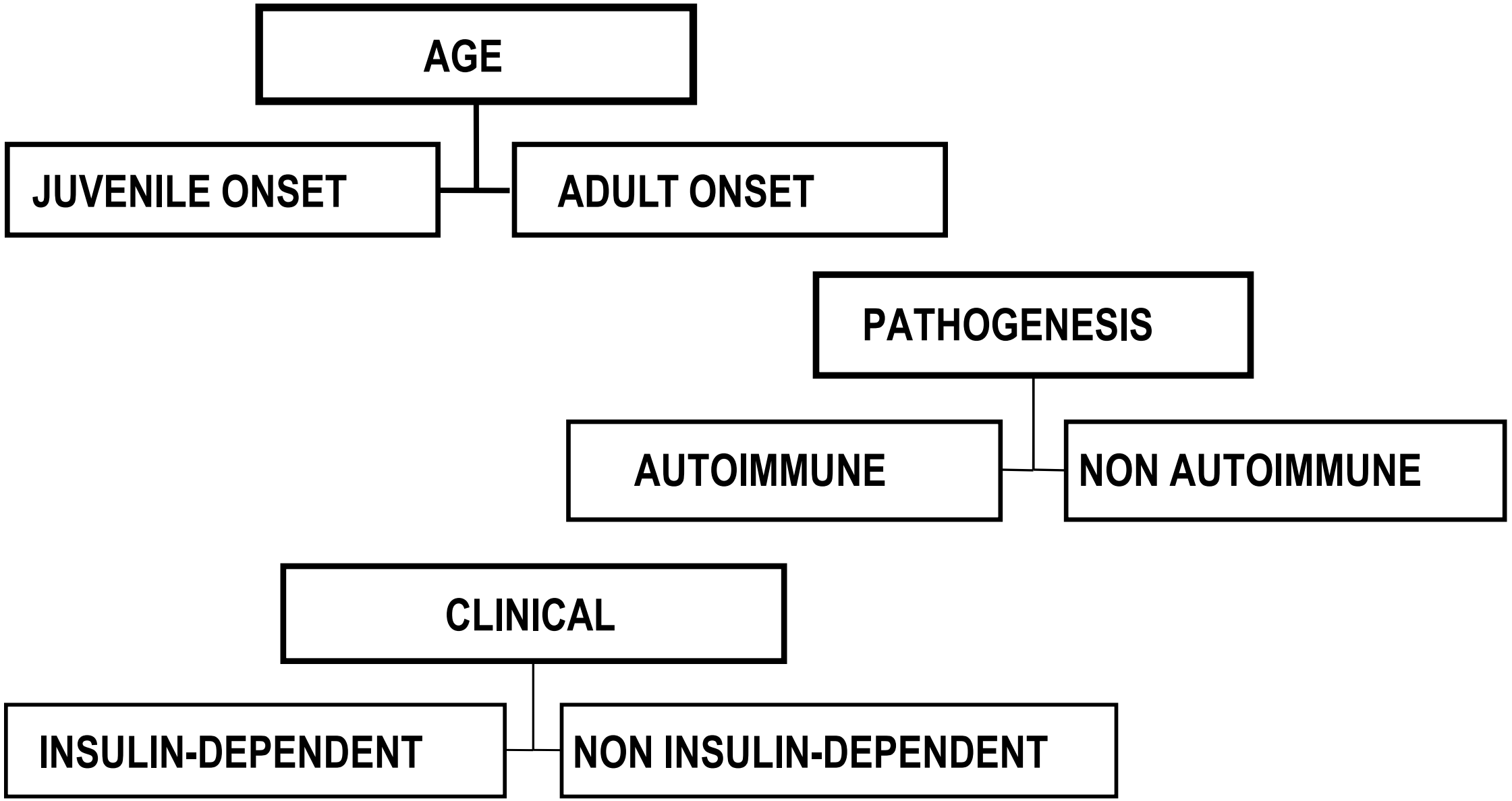
- Diabete monogenico

Old and new words

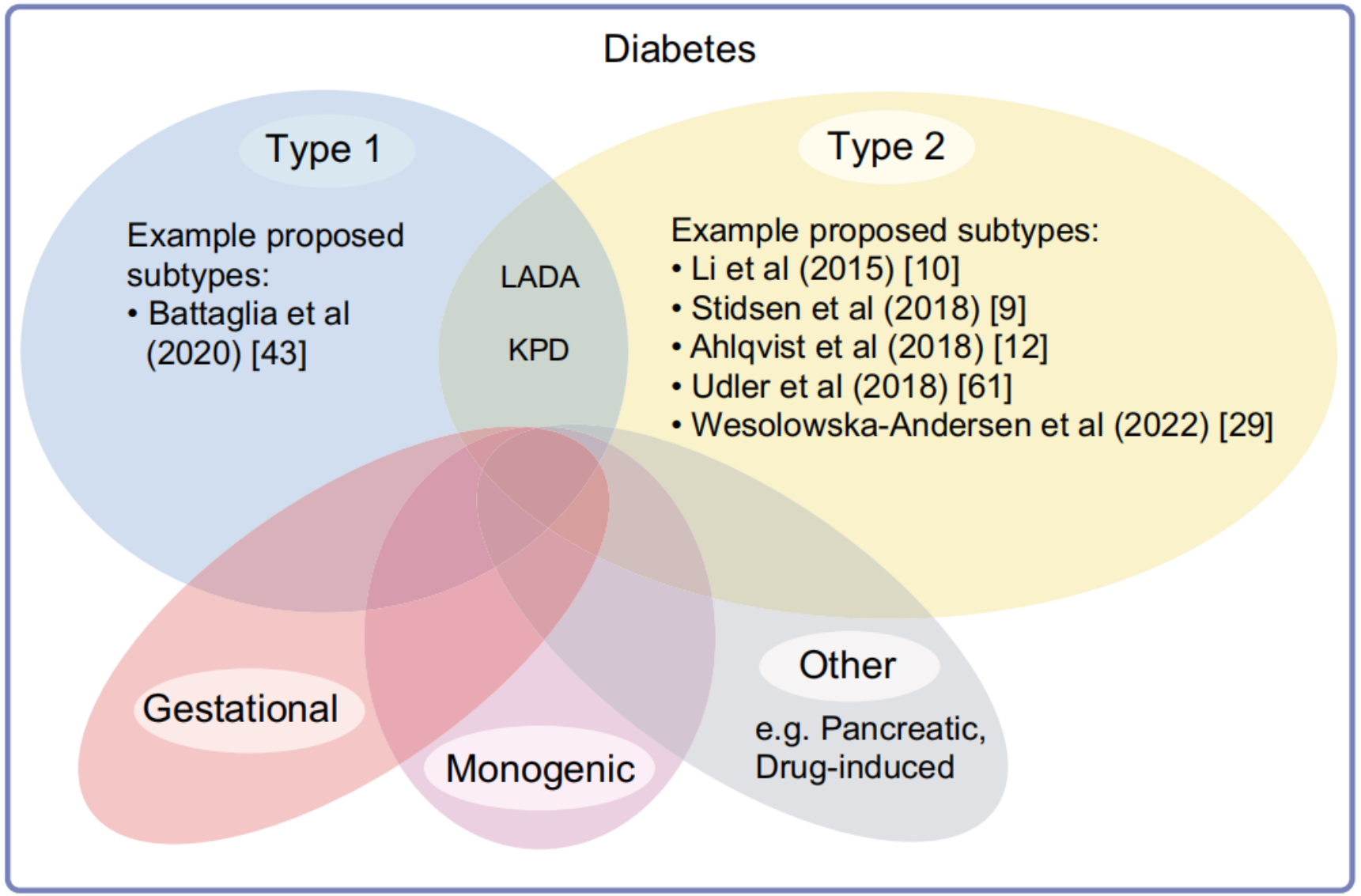
- **Phenotype:** cluster of observable properties, attempting to individualize disease expression in groups of patients
- **Endotype:** compilation of disease mechanisms explaining disease expression in groups of patients
- **Biomarker:** measurable indicator linking disease endotype with the phenotype
- **Prognotype:** prediction of outcome based on the disease endotype
- **Theratype:** prediction of treatment response based on the disease endotype

Agache I & Cezmi AA; JCI 2019

CLASSIFICATION OF DIABETES

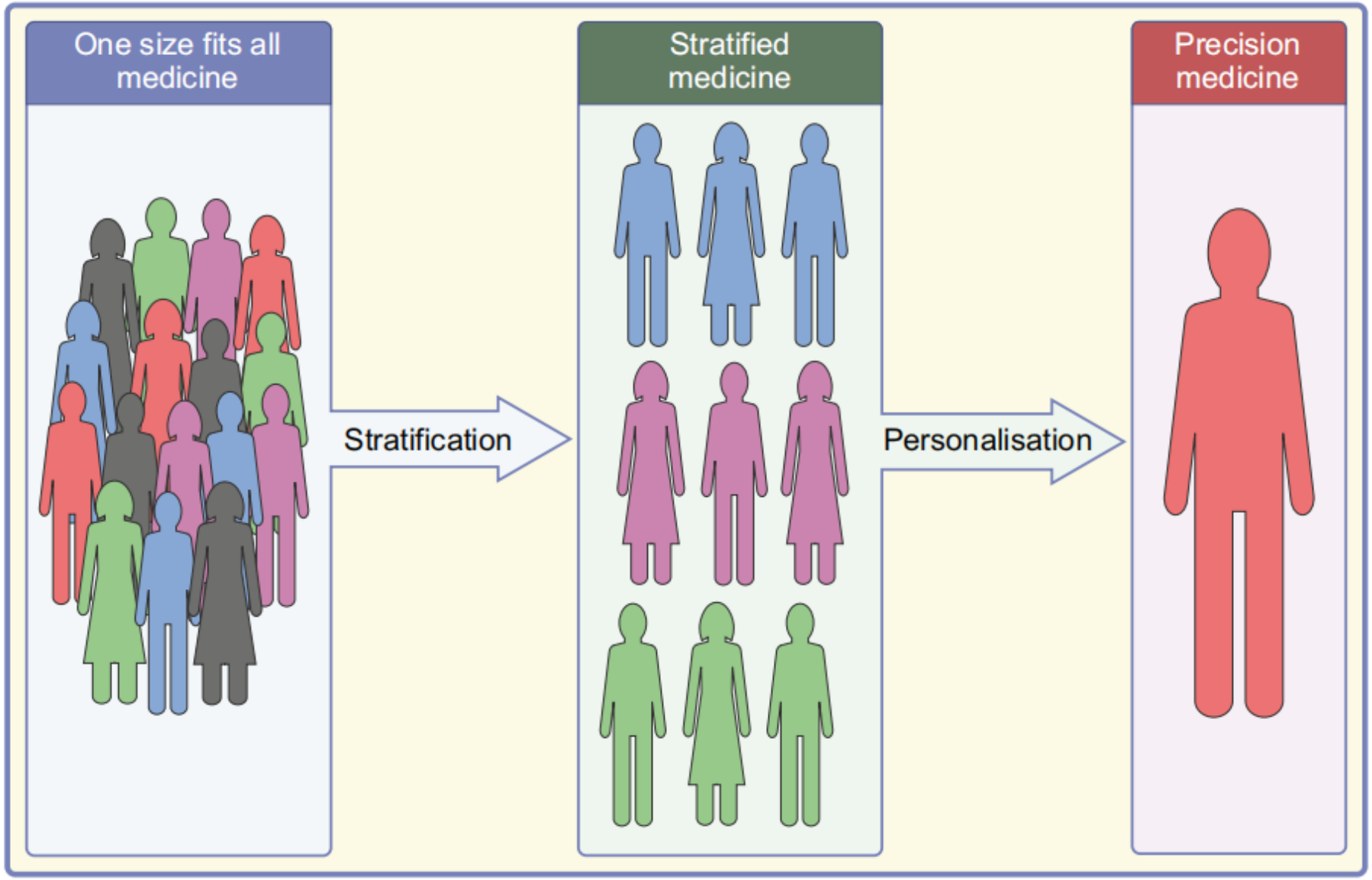


Diabetes Subtypes



Diabetologia (2022) 65:1758–1769

Precision medicine



Diabetologia (2022) 65:1913–1921

Precision Medicine: an updated definition

"Precision medicine focuses on minimizing errors and improving accuracy **in medical decisions** and health recommendations.

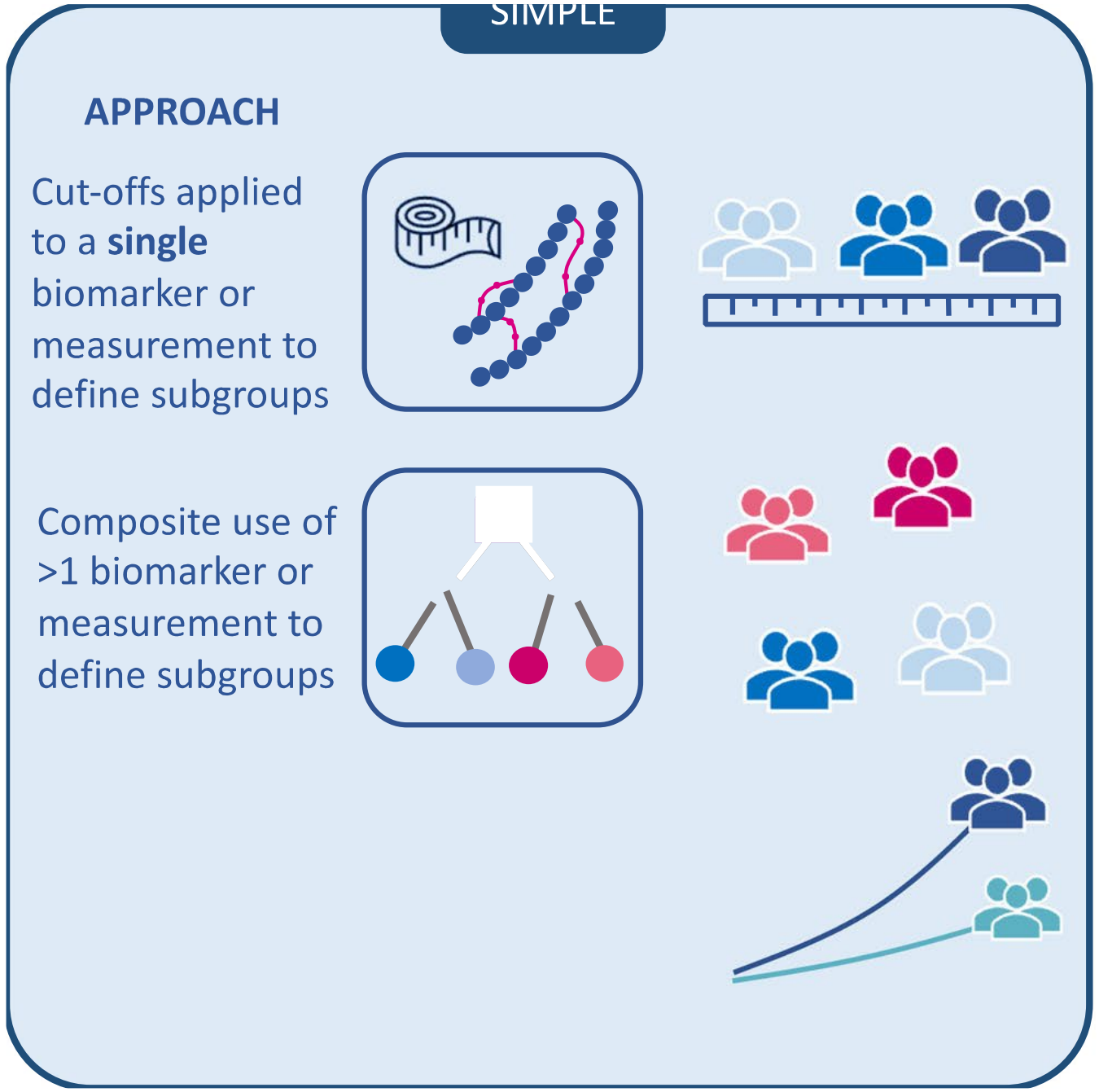
It seeks to maximize efficacy, cost-effectiveness, safety, access for those in need and compliance compared with contemporary evidence-based medicine.

Precision medicine emphasizes tailoring diagnostics or therapeutics (prevention or treatment) to subgroups of populations sharing similar characteristics."

Tobias DK et al.; Nature Med 2023

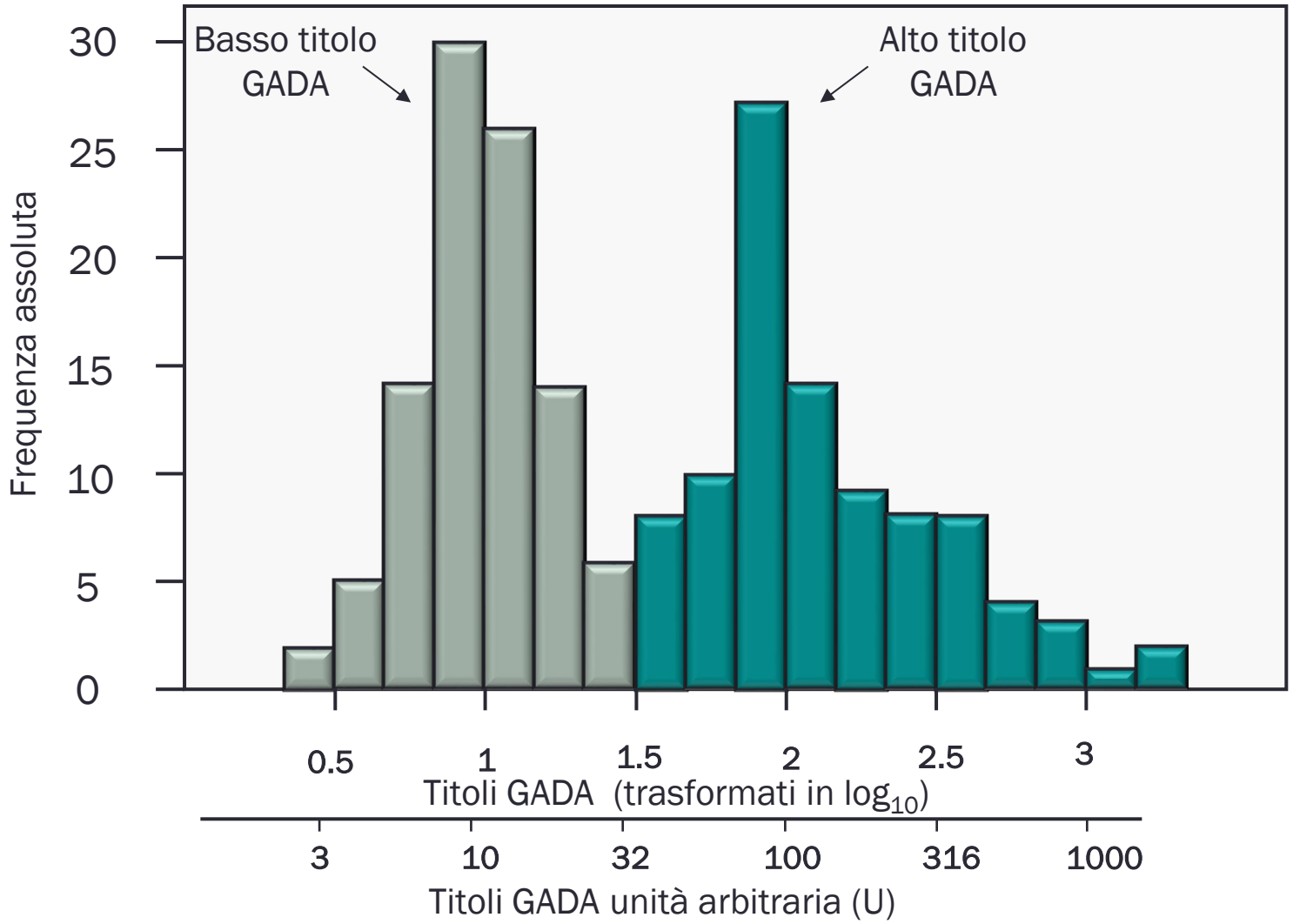
Schematic overview of the simple approach used to classify diabetes

(Misra S et al.; Communications Med 2023)



Distribuzione bimodale del titolo degli anticorpi GADA in 191 pazienti NIRAD

Buzzetti R et al (NIRAD 1), Diabetes Care , 2007



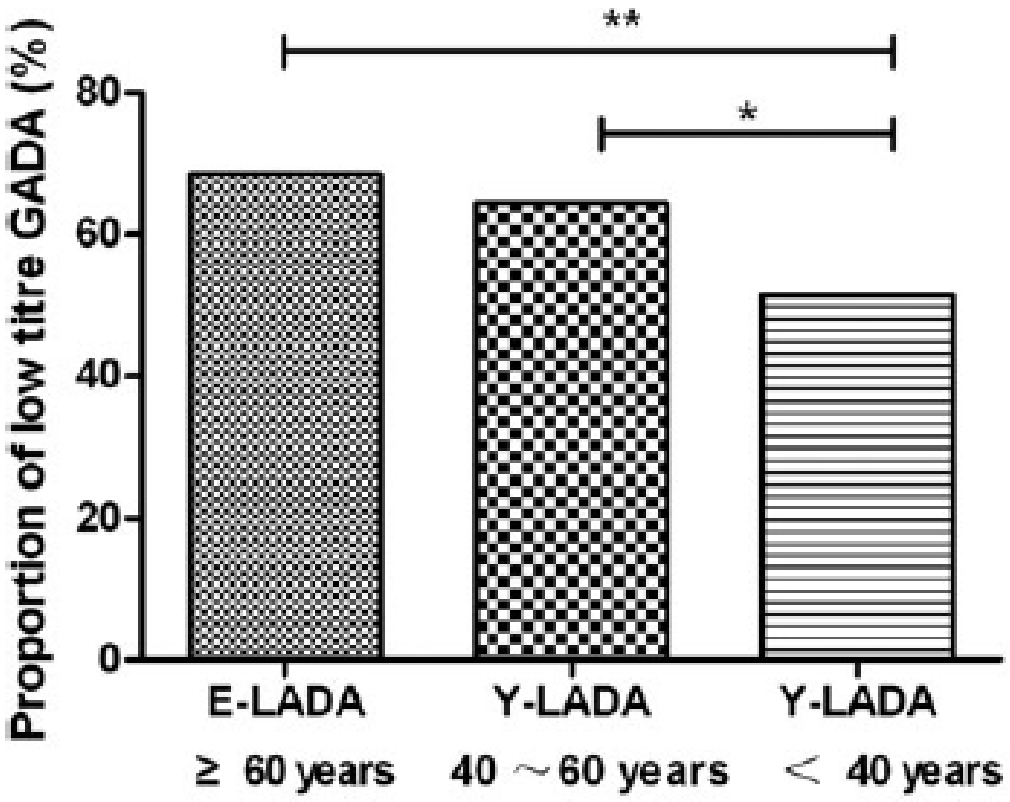
Caratteristiche cliniche dei pazienti con diabete autoimmune con alto e basso titolo GADA ed in T2DM

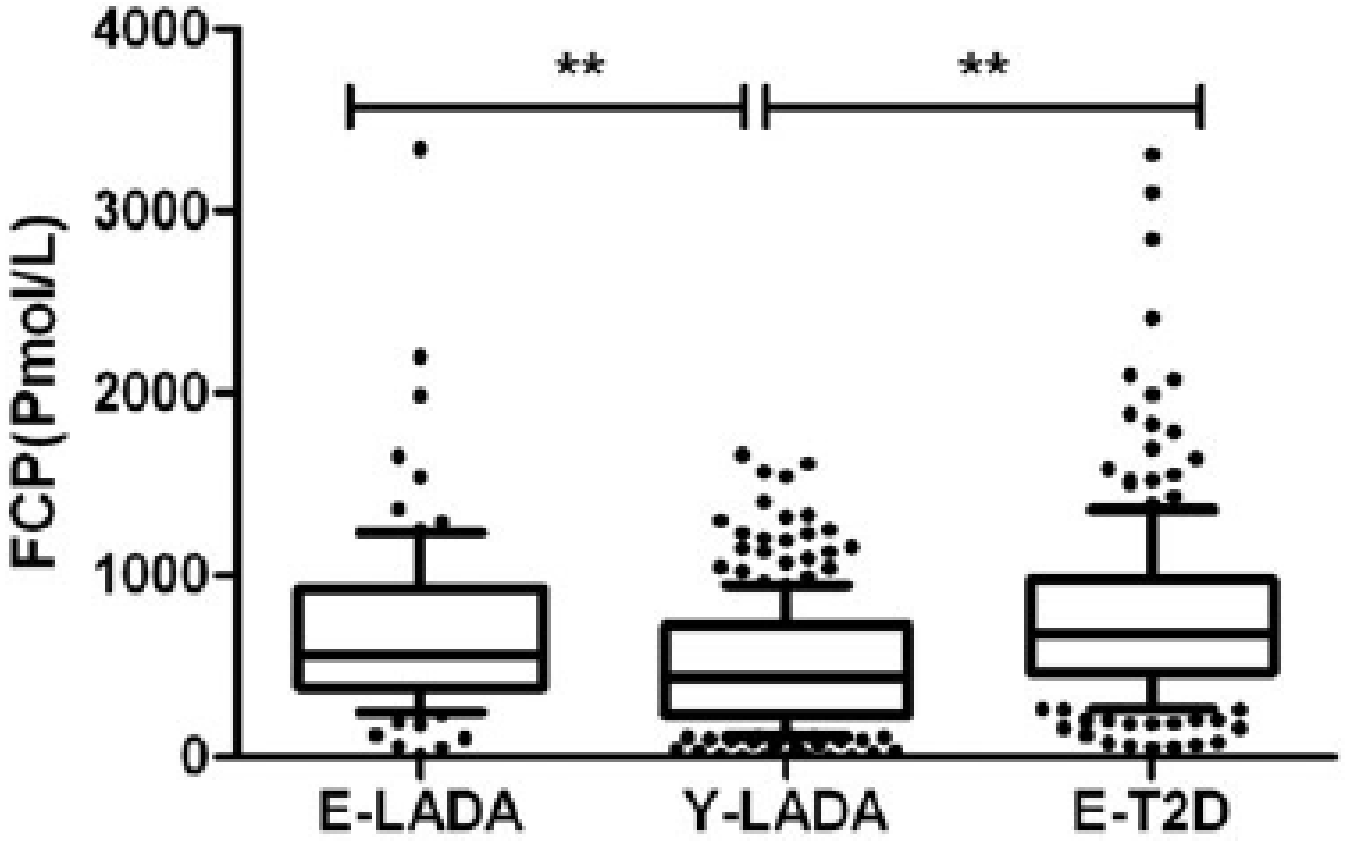
Buzzetti R et al (NIRAD 1), Diabetes Care, 2007

	high GADA titer	low GADA titer	T2DM	p for trend
n (Male/Female)	49/45	50/47	2100/1947	
Age of diagnosis (years)	49.1 ± 12.29	51.5 ± 13.13	55.6 ± 10.81	<0.001
HbA_1c (%)	7.8 ± 1.7	7.2 ± 1.8	6.8 ± 1.6	<0.001
BMI ($Kg/m^{2)}$	26.29 ± 5.16	28.43 ± 5.01	29.9 ± 5.4	<0.001
Waist circumference (cm)	92.86 ± 12.6	96.37 ± 13.37	101 ± 13.29	<0.001
Fasting glucose (mg/dl)	170.4 ± 63.4	166 ± 53	149.38 ± 44.47	<0.001
Triglycerides (mg/dl)	116 ± 106	171 ± 102	161 ± 119	
HDL (mg/dl)	49.7 ± 14.4	50.5 ± 12.3	47.7 ± 12.5	
Total cholesterol (mg/dl)	186 ± 44.8	207 ± 47	209 ± 43.3	
Uric Acid (mg/dl)	4.38 ± 1.71	4.62 ± 1.16	5.13 ± 1.44	<0.001

* Data are given as means and standard deviation.
All comparisons are adjusted for age of recruitment, duration of disease, gender and therapy.
Triglycerides were also corrected for Hb1Ac.

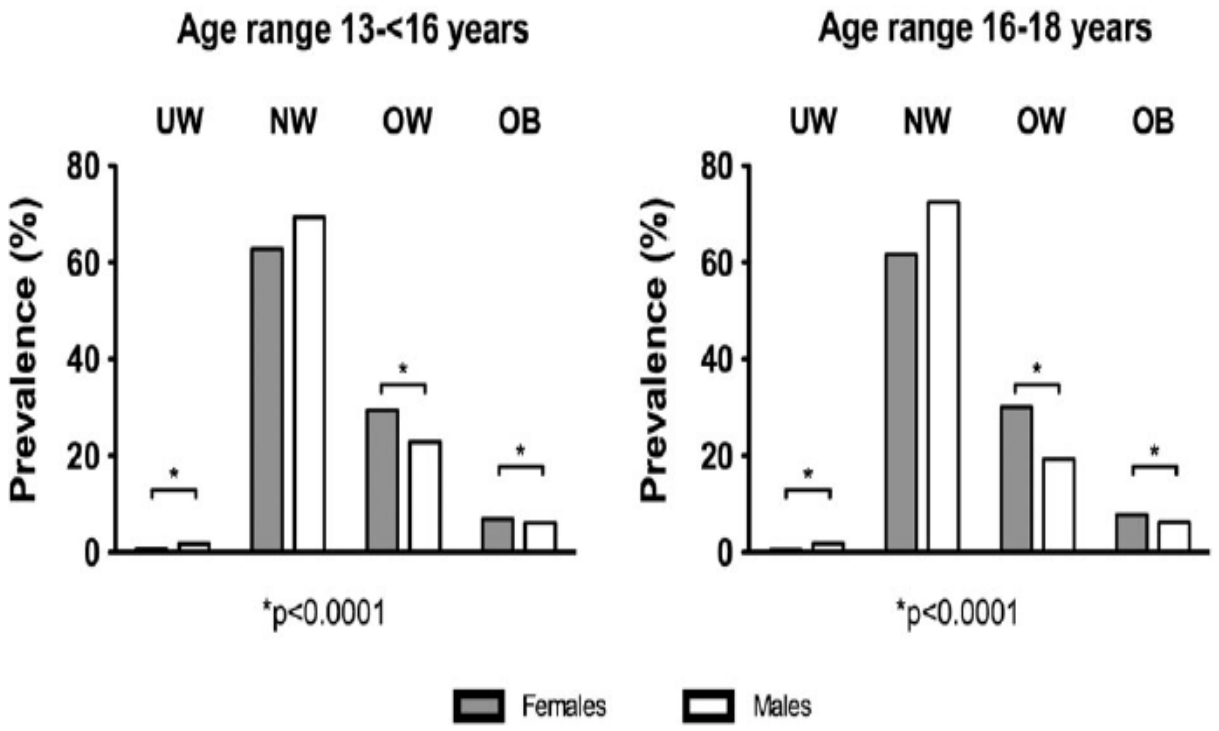
Low GADA titre and c-peptide

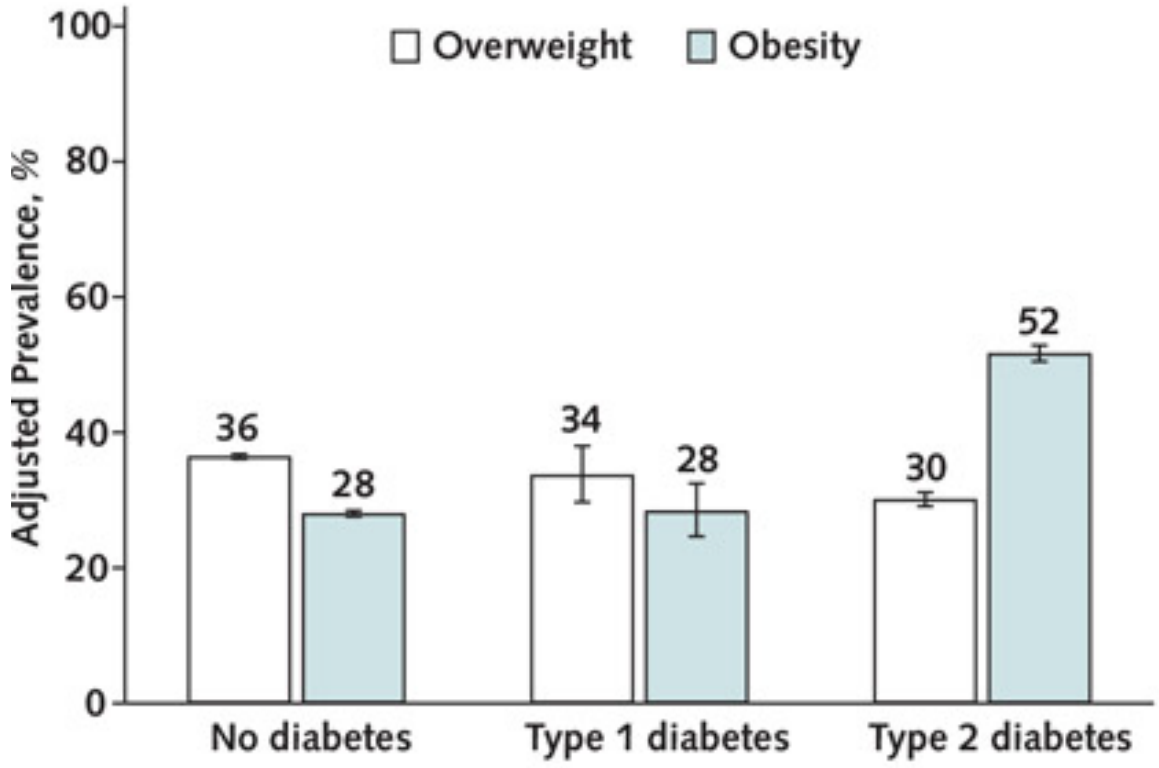




Niu X et al. Diabetes Metab Res Rev. 2019;35:e3068

Prevalence of Overweight and Obesity in young and adult patients with type 1 diabetes

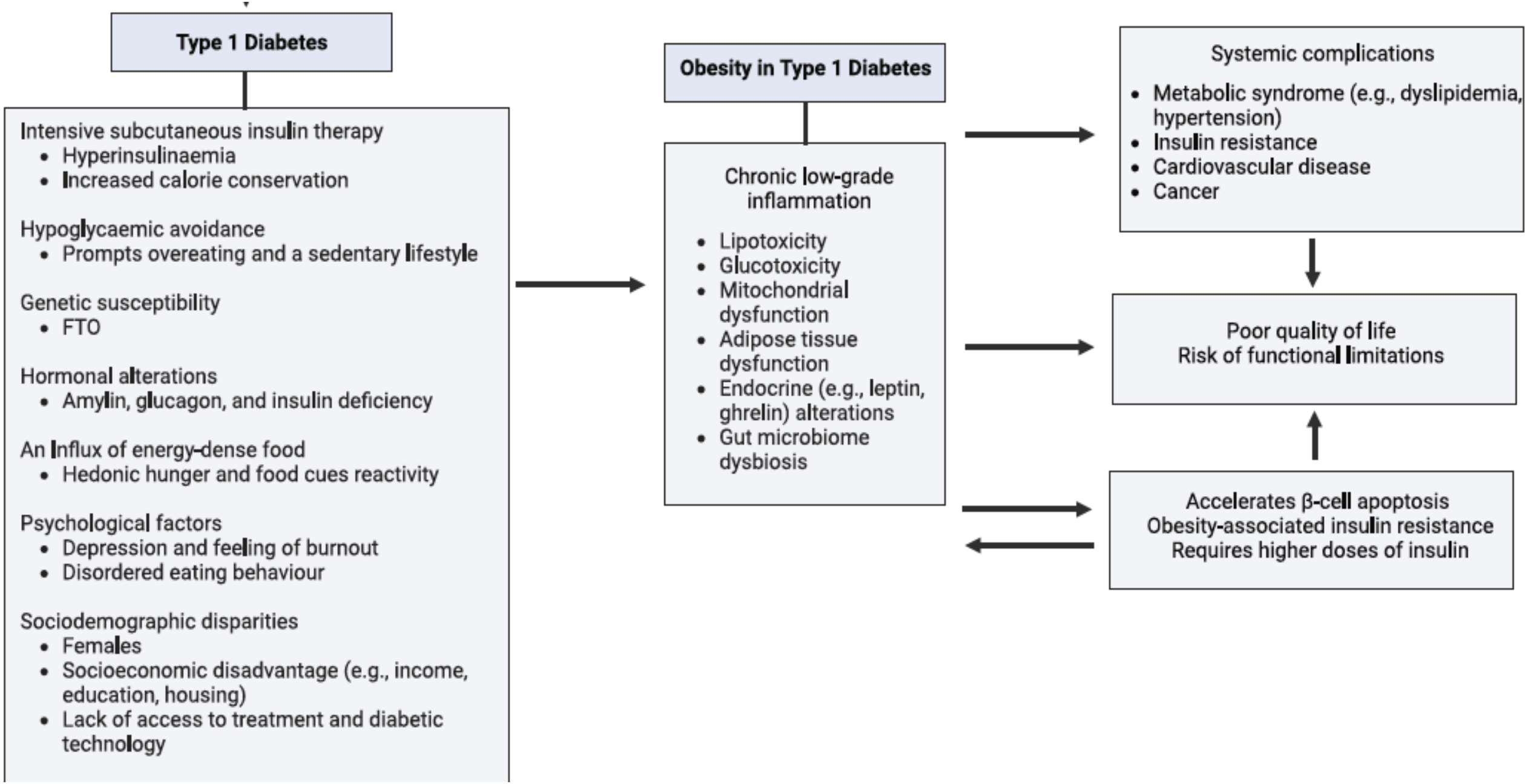




Overall prevalence of OW, and Ob was: 22.3%, and 7.3% in males and 27.2%, and 6.8% in females

Maffeis C et al. Ped Diab 2018

Fang M et al. Ann Intern Med. 2023


Type 1 Diabetes
Intensive subcutaneous insulin therapy
• Hyperinsulinaemia
• Increased calorie conservation
Hypoglycaemic avoidance
• Prompts overeating and a sedentary lifestyle
Genetic susceptibility
• FTO
Hormonal alterations
• Amylin, glucagon, and insulin deficiency
An influx of energy-dense food
• Hedonic hunger and food cues reactivity
Psychological factors
• Depression and feeling of burnout
• Disordered eating behaviour
Sociodemographic disparities
• Females
• Socioeconomic disadvantage (e.g., income, education, housing)
• Lack of access to treatment and diabetic technology
Obesity in Type 1 Diabetes
Chronic low-grade inflammation
• Lipotoxicity
• Glucotoxicity
• Mitochondrial dysfunction
• Adipose tissue dysfunction
• Endocrine (e.g., leptin, ghrelin) alterations
• Gut microbiome dysbiosis
Systemic complications
• Metabolic syndrome (e.g., dyslipidemia, hypertension)
• Insulin resistance
• Cardiovascular disease
• Cancer
Poor quality of life
Risk of functional limitations
Accelerates β-cell apoptosis
Obesity-associated insulin resistance
Requires higher doses of insulin

Clinical and Safety Outcomes With GLP-1 Receptor Agonists and SGLT2 Inhibitors in Type 1 Diabetes: A Real-World Study

Khary Edwards,[1,*] Xilong Li,[2,*] and Ildiko Lingvay[1,2]

The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, 920–930

Table 3. Change in outcomes over 12 months of GLP-1RA/SGTL2i use

104 patients with T1DM	GLP-1RA	SGLT2i	Between-group P^a
HbA_{1c}, %			
Baseline	7.7 (7.4-8.0)	7.9 (7.5- 8.4)	
12 mo	7.3 (7.0-7.7)	7.3 (6.9-7.7)	
P (within-group change over 12 mo)	.007	< .001	.248
Weight, kg			
Baseline	90.4 (85.3-95.8)	89.2 (82.1-96.9)	
12 mo	85.4 (80.3-90.8)	87.5 (80.1-95.5)	
P (within-group change over 12 mo)	< .001	.168	.027
TDD insulin, units			
Baseline	61.8 (53.3-71.7)	58.0 (47.5-71.5)	
12 mo	49.9 (42.4-58.8)	57.0 (44.3-72.3)	
P (within-group change over 12 mo)	< .001	0.798	.073
Basal insulin, units			
Baseline	30.7 (27.1-34.7)	31.3 (26.2-37.5)	
12 mo	26.0 (22.6-29.8)	25.6 (21.0-31.3)	
P (within-group change over 12 mo)	< .001	.003	.689
Bolus insulin, units			
Baseline	37.9 (30.6-45.1)	32.9 (22.5-43.4)	
12 mo	27.9 (19.5-36.1)	35.0 (22.1-47.8)	
P (within-group change over 12 mo)	.004	.719	.068

Changes in weight (A), HbA1c (B), total daily dose of insulin (TDD) insulin (C), and bolus insulin (D) from baseline to 12 months between GLP-1RA and SGLT2i

A B

Table 4. Adverse events experienced during GLP-1RA or SGLT2i use

Event	GLP-1RA (N = 76)		SGLT2i (N = 39)	
	% (n)[a]	Rate[b]	% (n)	Rate[b]
DKA	3.9 (3)	1.6	12.8 (5)	6.6
Severe hypoglycemia	1.3 (1)	0.5	2.6 (1)	0
Pancreatitis	0 (0)	0	0 (0)	1.1
Hospitalizations[c]	21.1 (16)	13.6	28.2 (11)	15.4
Emergency room visits[c]	19.7 (15)	13.6	7.7 (3)	3.3

Precision subclassification of type 2 diabetes: a systematic review

Misra S et al. COMMUNICATIONS MEDICINE | (2023) 3:138Mi

- The **51 studies using simple type 2 diabetes subclassification** approaches incorporated 1,751,350 participants with prevalent or new-onset type 2 diabetes.
- Approximately half the studies had a **prospective design** (25/51), the remaining half had a **cross-sectional** (26/51) design. For longitudinal studies, study follow-up periods ranged from <1 year to 22 years.
- Simple approaches to subclassification included urine and blood biomarkers, **anthropometric measures**, clinical data such as **age at diagnosis**, surrogate **beta-cell metrics** derived from blood C-peptide or insulin along with other less diabetes-related biomarkers such as bilirubin levels or pulse wave velocity.

Precision subclassification of type 2 diabetes: a systematic review

Misra S et al. COMMUNICATIONS MEDICINE | (2023) 3:138Mi

- Use of simple approaches to subclassify type 2 diabetes:
  - The associations of stratified exposure characteristics were investigated with various outcomes: 1) measures of glycaemia, 2) clinical characteristics, 3) measures of diabetes progression such as time-to-insulin treatment or development of microvascular complications and 4) cardiovascular outcomes and/or mortality.
  - **No study** evaluating a simple approach to type 2 diabetes subtyping has been **adequately reproduced**, although some studies identified biologically plausible subgroups.
  - For example, subclassifications derived using BMI, beta-cell function, lipid profiles, and age appeared to be associated with some outcomes that could be helpful in clinical practice. These potential subclassifications need to be replicated in better-designed studies

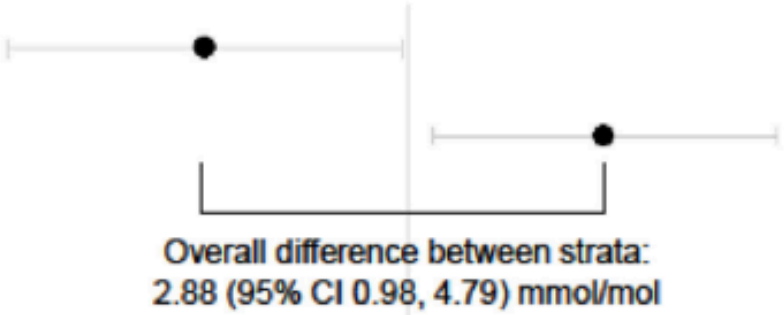
The two main hypotheses tested in the TriMaster trial: results on HbA1c

a) Hypothesis 1 - Pioglitazone v Sitagliptin

Stratfication by BMI

BMI<=30 (n=141)

BMI>30 (n=215)

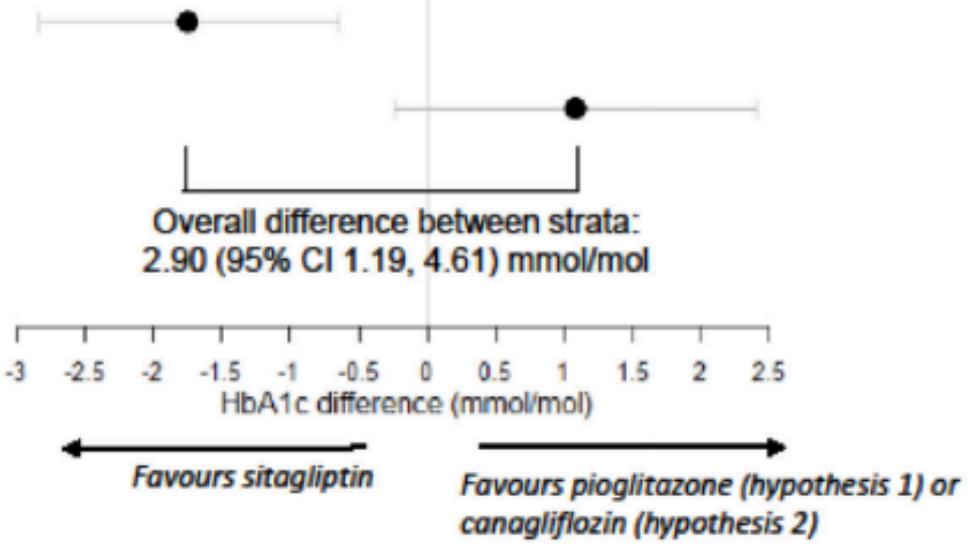


b) Hypothesis 2 - Canagliflozin v Sitagliptin

Stratification by renal function

eGFR 60-90 (n=163)

eGFR>90 (n=179)



Shields BM et al.; Nature Med 2023

Primary take-home message of the TriMaster trial

	Ranks of preference of anti-diabetes drugs as add-on to metformin			
BMI (kg/m^2)	< 30		≥ 30	
eGFR (ml/min/1.73 m^2)	> 90	60 - 90	> 90	60 - 90
1st Drug	Canagliflozin	Sitagliptin	Pio or Cana	Pioglitazone

Small effects on HbA1c,
no consideration of protection
from target organ damage

from Shields BM et al.; Nature Med 2023

Schematic overview of the complex approach used to classify type 2 diabetes

(Misra S et al.; Communications Med 2023)

Diabete tipo 2 e fenotipi

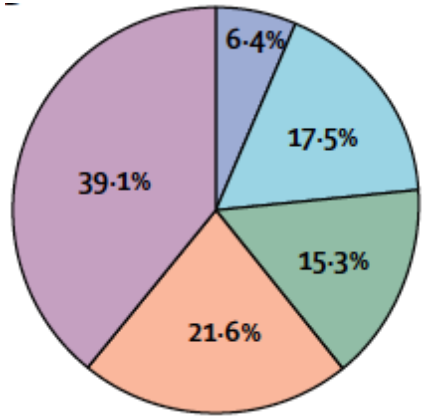
Età di esordio | BMI | HbA1c | GADA | HOMA2_B* | HOMA2_IR*

GADA+

Si → CLUSTER 1
Severe Autoimmune Diabetes (SAID)

No → K-means clustering

9000 pazienti
svedesi con diabete neo-diagnosticato
ANDIS cohort



CLUSTER 2
Severe Insulin-Deficient Diabetes (SIDD)
- ↓ Età di esordio
- ↓ BMI
- ↑ HbA1c
- ↓ HOMA2_B

CLUSTER 3
Severe Insulin-Resistant Diabetes (SIRD)
- ↑ HOMA2_IR
- ↑ BMI
- ↑ Età di esordio

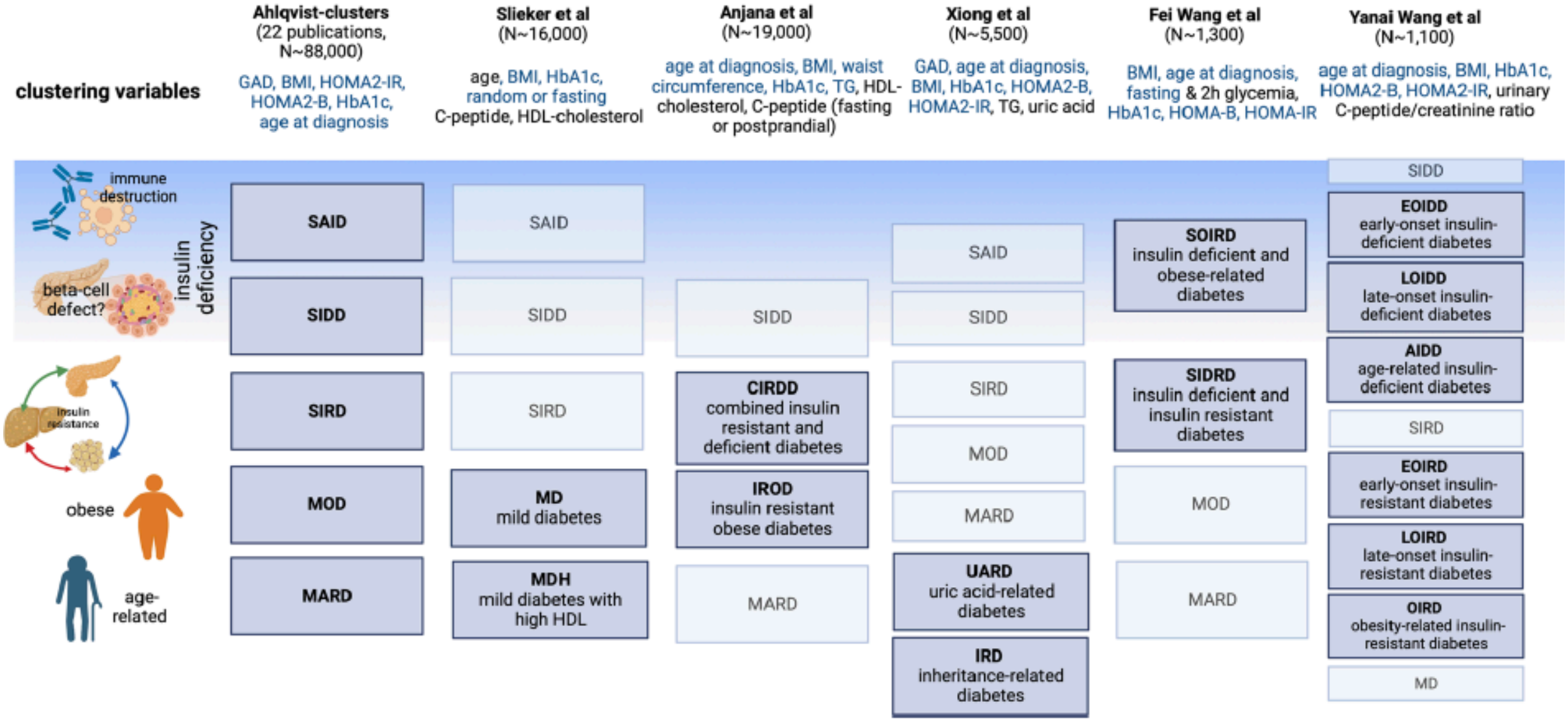
CLUSTER 4
Mild Obesity-Related Diabetes (MOD)
- Lieve HOMA2_IR
- ↑ BMI

CLUSTER 5
Mild Age-Related Diabetes (MARD)
- Esordio in età avanzata
- Modeste alterazioni metaboliche

(*c-peptide)

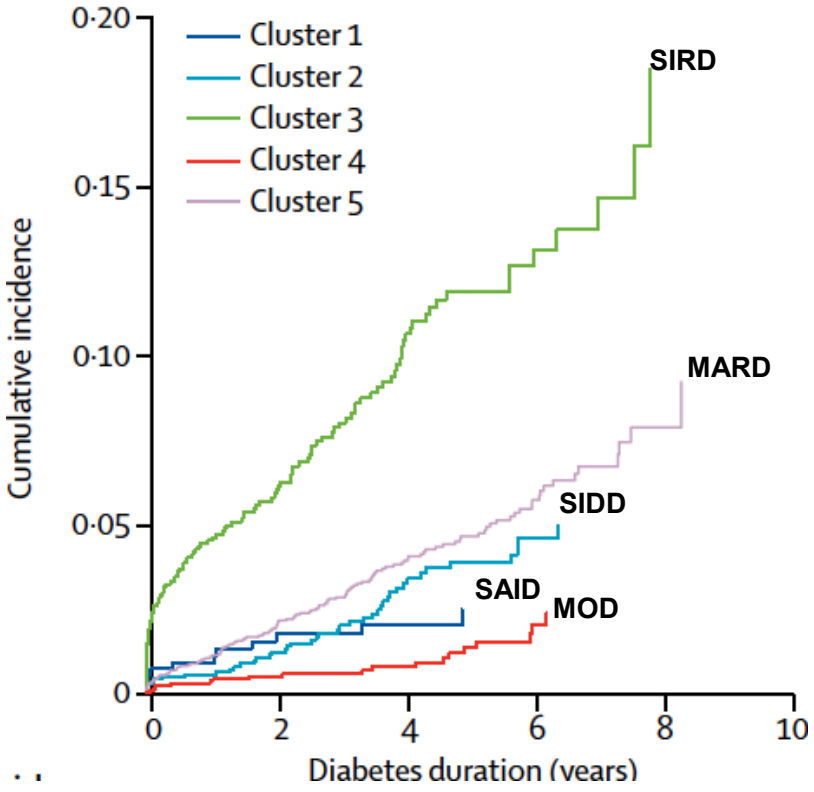
Ahlqvist E et al., *Lancet Diabetes Endocrinol* ,2018

Main characteristics of diabetes clusters

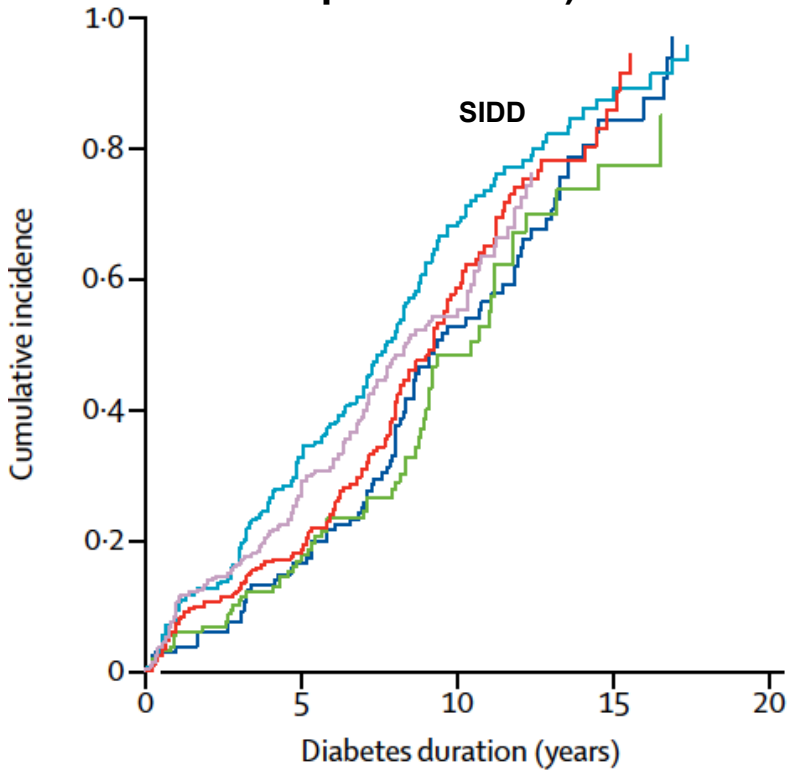


Clusters e rischio di complicanze

Time to chronic kidney disease (≥stage 3B)

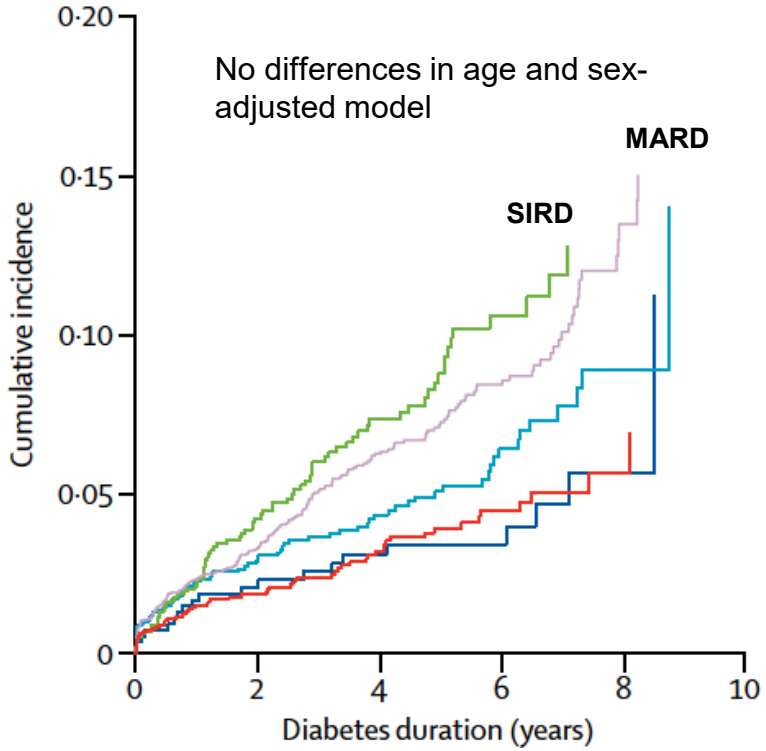


Time to diabetic retinopathy (mild-non-proliferative & proliferative)



Time to coronary events

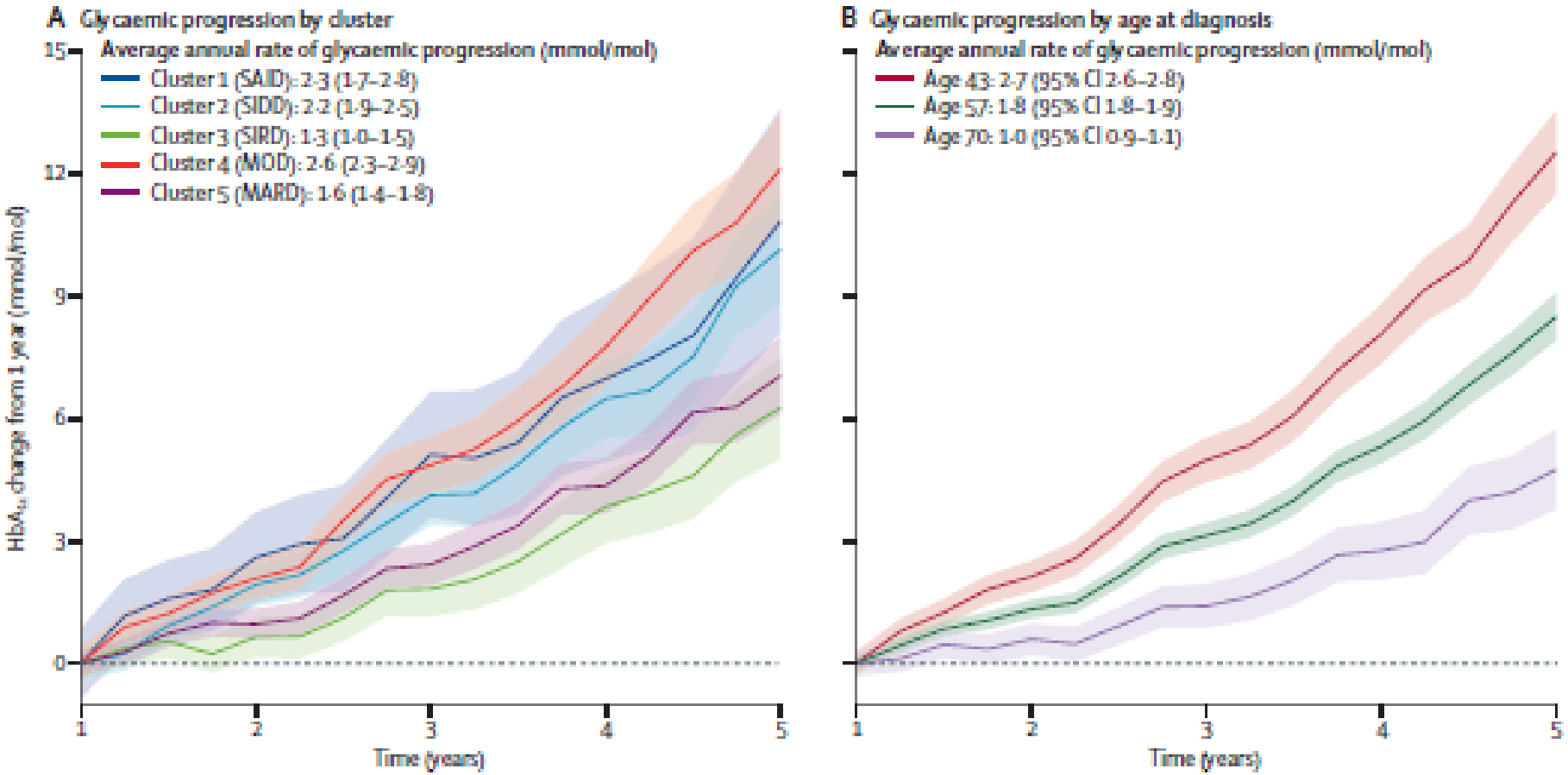
No differences in age and sex-adjusted model



Ahlqvist E et al., *Lancet Diabetes Endocrinol* 2018

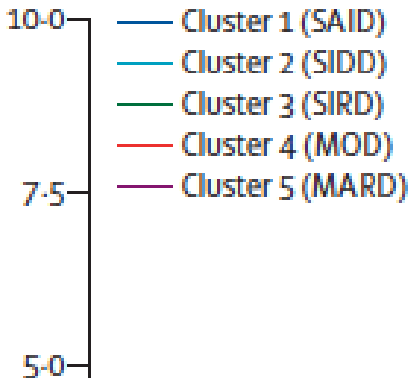
Approccio basato sui clusters o su semplici caratteristiche cliniche?

L'utilizzo di un modello basato su semplici caratteristiche cliniche,ottiene risultati sovrapponibili rispetto ai clusters nella predizione delle complicanze (età all'esordio per la progressione del diabete)



Dennis J.M et al, *Lancet Diabetes Endocrinol*, 2019

Renal progression by cluster in ADOPT over 5 years



	Participants	Person-years at risk	Events	Unadjusted HR (95% CI)	HR (95% CI)
Time to CKD stage 3 (n=3694)					
Cluster 1 (SAID)	155	499	6	2·82 (1·02–7·75)	1·56 (0·56–4·29)*

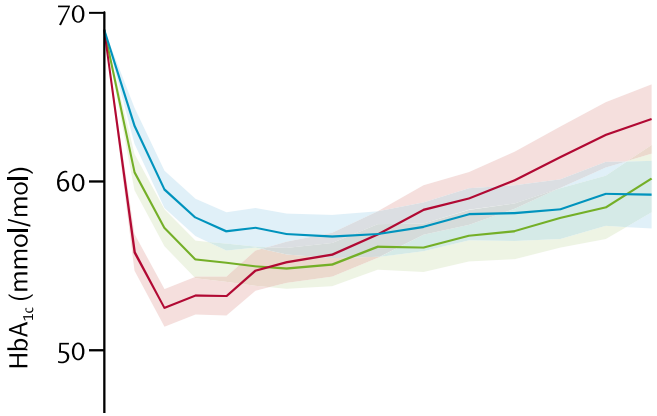
In ADOPT and RECORD, baseline eGFR explained a greater proportion of variation than did the clusters

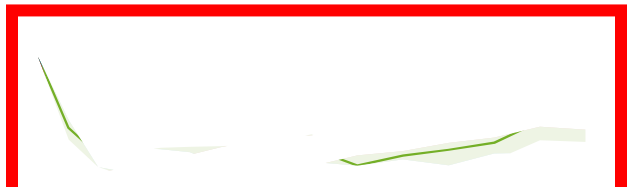
Estimated glomerular filtration rate at baseline was a better predictor of time to chronic kidney disease

n rate.

Dennis J.M et al, *Lancet Diabetes Endocrinol*, 2019

Can the four type 2 diabetes subtypes predict the response to therapy? The ADOPT trial: changes of HbA1c by drug for type 2 diabetes subtype over 3 years (n = 3607)



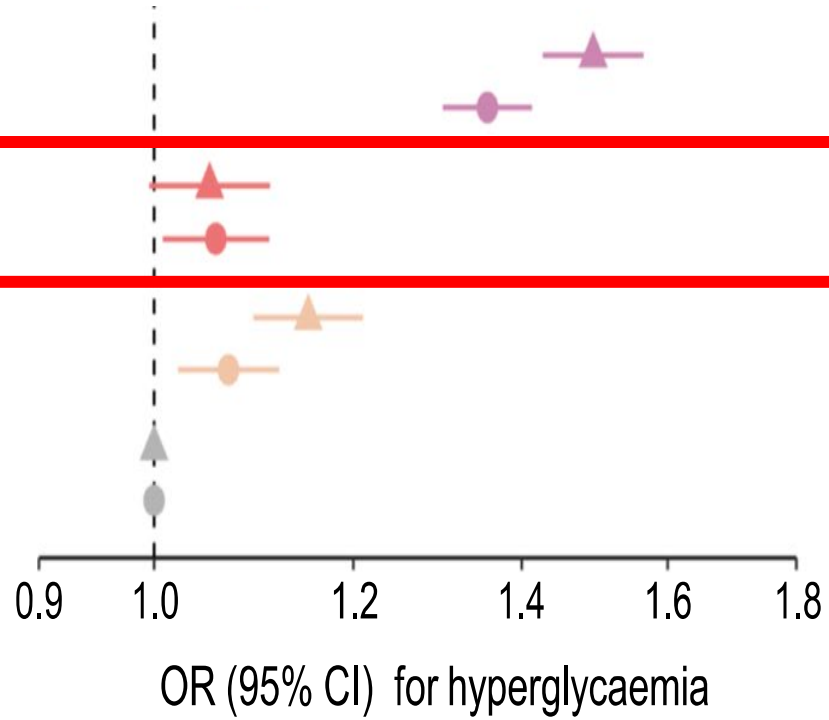


For treatment response we found that models combining four simple clinical measures (age, sex, baseline HbA1c, and BMI) explained more variation in response than did the clusters..

Dennis JM et al.;
Lancet Diabetes & Endocrinol 2019

Can the four type 2 diabetes subtypes predict the response to therapy? The ORIGIN trial: odds ratio of hyperglycemia in the standard care vs glargine treated arm by type 2 diabetes subtype

Cluster	Intervention	*n*	Adjusted OR	*p*	*p* interaction cluster × intervention
SIDD	standard care	791	1.49 (1.43, 1.57)	$< 2.0\times10^{-16}$	0.001
	glargine	803	1.36 (1.30, 1.41)	$< 2.0\times10^{-16}$	
SIRD	standard care	455	1.05 (1.00, 1.11)	0.07	0.83
	glargine	459	1.06 (1.01, 1.11)	0.02	
MOD	standard care	833	1.16 (1.10, 1.22)	3.86×10^{-6}	0.006
	glargine	762	1.07 (1.02, 1.12)	0.004	
MARD	standard care	1323	REF	REF	REF
	glargine	1350	REF	REF	



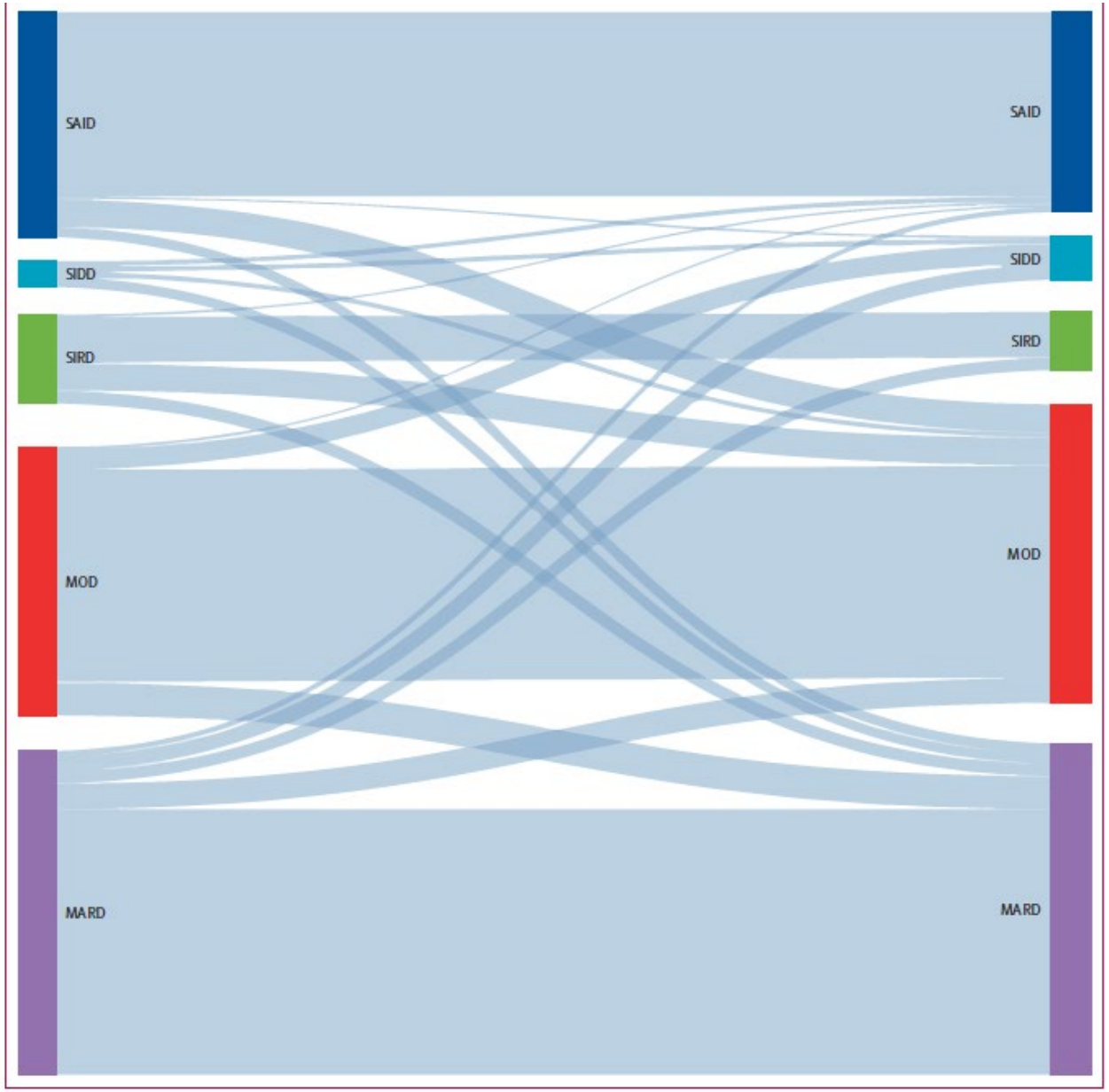
3/SIRD
4/MOD
5/MARD
glargine
standard care

Pigeyre M et al.; Diabetologia 2022

Cluster redistribution at 5-year follow-up

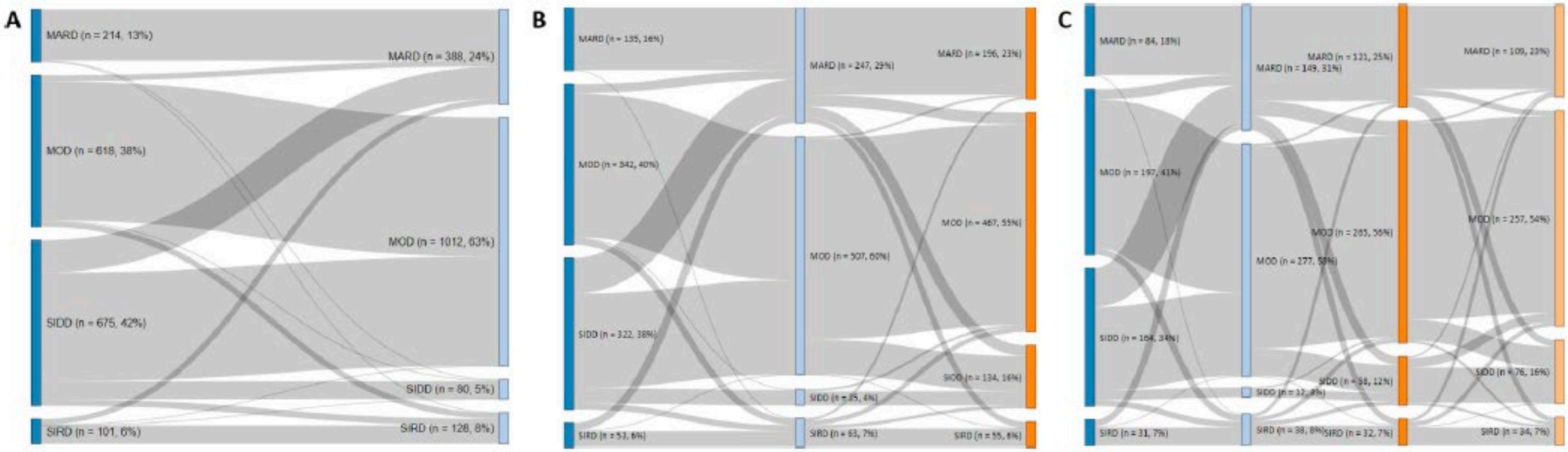
Cluster reproducibility at follow-up (ie, the proportion of patients allocated to the same cluster at baseline and follow up) was 20% SIDD, 82% SAID, 51% SIRD, 79% MOD, and 82% MARD

(1105 patients with newly diagnosed type 1 or type 2 diabetes)



Zaharia OP et al. Lancet Diabetes Endocrinol 2019

Cluster redistribution after 3 months (A, n=1680), 1 year (B, n=852) and 2 years (C, n=476) of an intensive multidisciplinary intervention



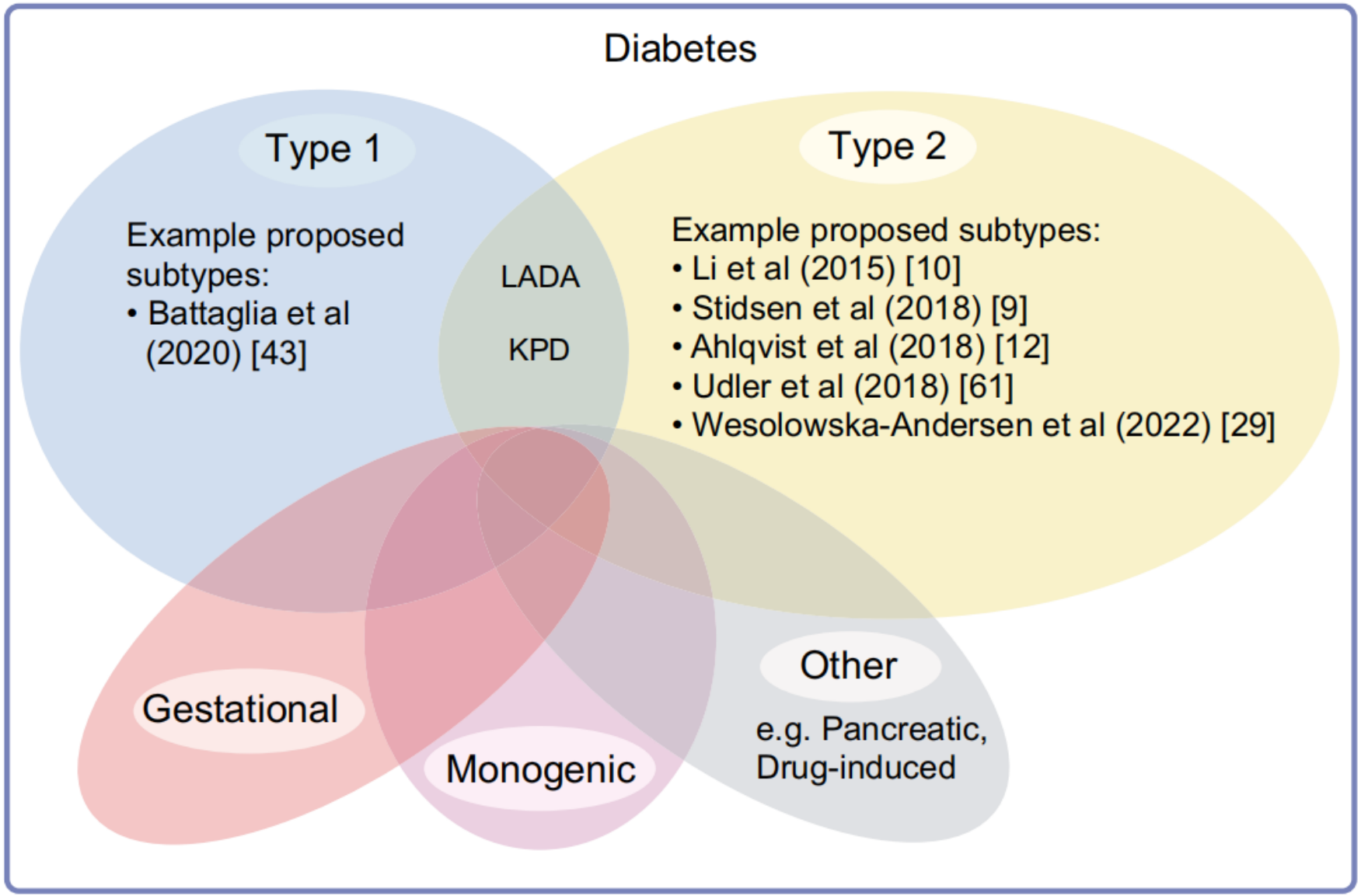
Only 10.7% of SIDD subjects remained in this subgroup and most were reclassified to either MOD (65.8%) or MARD (19.5%) at the 3-month time point, whereas other groups remained relatively stable over time (MARD 97.7%, MOD 91.6% and SIRD 74.2%;

AL I NodmCh a Qdr B` qd 1/ 1/ :7

Medicina di precisione per la diagnosi e terapia del diabete di tipo 2

- **L'approccio della medicina di precisione per la diagnosi e terapia del diabete di tipo 2 al momento potrebbe dare risultati inferiori alle attese.**
- **Il trial TriMaster** (un esempio di approccio semplice alla terapia anti-diabete di precisione) **è stato metodologicamente riuscito, ma minimamente significativo dal punto di vista clinico.**
- **La classificazione del T2DM secondo Ahlqvist et al.** (approccio complesso: hard clustering rigoroso basato su solo 5 fenotipi) **è stata riprodotta da altri gruppi di ricerca e in altre etnie.**
- **L'approccio di Ahlqvist** sarebbe fattibile nella pratica clinica quotidiana.
- **Rimane da determinare se uno di questi approcci di clustering riveli veri endotipi.**
- **Dovrebbero essere condotti GWAS specifici per cluster.**
- **Dovrebbero essere eseguiti RCT informati dai cluster** (o dovrebbero essere recuperati più RCT).

Diabetes Subtypes



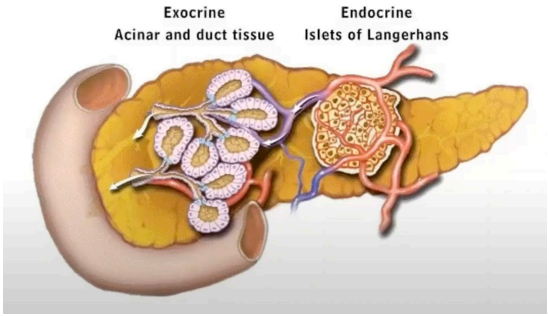
Diabetologia (2022) 65:1758–1769

Diabete Pancreatico

Terminologia

- Diabete pancreatico
- Diabete Pancreatogenico
- Diabete Tipo 3c
- DEP - *diabetes of the exocrine pancreas*

Riferiti a diabete causato da patologie del pancreas esocrino



Type 3c diabetes

Table 1 Current classification of diabetes mellitus

I	Type 1 Diabetes Mellitus (β-cell destruction, usually leading to absolute insulin deficiency)
	A: Immune mediated
	B: Idiopathic
II	Type 2 Diabetes Mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III	Other Specific Types Of Diabetes Mellitus
	A: Genetic defects of β-cell function
	B: Genetic defects in insulin action
	C: Diseases of the exocrine pancreas
	1: Pancreatitis
	2: Trauma/pancreatectomy
	3: Neoplasia
	4: Cystic fibrosis
	5: Hemochromatosis
	6: Fibrocalculous pancreatopathy
	7: Others
	D: Endocrinopathies
	E: Drug- or chemical-induced
	F: Infections
	G: Uncommon forms of immune-mediated diabetes
	H: Other genetic syndromes sometimes associated with diabetes
IV	Gestational Diabetes Mellitus

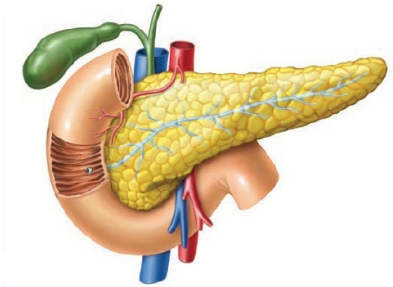
Lancet Gastroenterol Hepatol. 2016 November ; 1(3): 226–237. doi:10.1016/S2468-1253(16)30106-6.

Causes of type 3c diabetes mellitus

Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer

Causes

- Pancreatitis (acute or chronic)
- Pancreatectomy
- Pancreatic carcinoma
- Cystic fibrosis
- Haemochromatosis



Lancet Gastroenterol Hepatol. 2016 1(3): 226–237.

Epidemiologia

- Incidenza e prevalenza difficili da stabilire
- Probabilmente più frequente di quanto generalmente riportato
  - Mancanza di linee guida condivise
  - Difficoltà nella diagnosi corretta
  - Pancreatite cronica non diagnosticata
  - Sovrapposizione con altri tipi di DM
- La prevalenza di diabete pancreatico riportata dai diversi studi varia dall'1% al 9% dei casi di diabete

diabetes in exocrine pancreatic diseases

- CP overall 30%, up to 85% after 25 years) *(Zhu et al Pancreas 2019)*
- AP overall 23%, 37% after 5 years *(Zhy et al. Front Physiol 2019)*
- CF about 20% of adolescents and 40–50% of adults
- PC 30% new onset diabetes in pancreatic cancer patients (may be the first manifestation of PC)

NICE Guidance (NG17)
For people **aged 60** and over presenting with **weight loss and new-onset diabetes**, follow recommendations on assessing for pancreatic cancer in the section on pancreatic cancer in the NICE guideline on suspected cancer: recognition and referral. [2022]

CRITERI DIAGNOSTICI

Al momento non esistono criteri diagnostici condivisi per il diabete pancreatico.

Sono stati proposti i seguenti criteri attualmente più utilizzati (*Ewald&Bretzel EJIM 2013)*

Criteri diagnostici maggiori (devono essere tutti rispettati)

Diagnosi di diabete mellito+

- Presenza di insufficienza del pancreas esocrino (utilizzando **l'elastasi** fecale o i test funzionali).
- Diagnostica per immagini pancreatica patologica (ecoendoscopia, RMN, TC)
- Assenza di autoimmunità associata al diabete mellito tipo 1.

Criteri diagnostici minori

- Compromissione della funzione beta-cellulare (es. HOMA-B, C-peptide).
  Non eccessiva insulino-resistenza (es. HOMA-IR).
  Compromissione della secrezione incretinica (es. GLP1, polipeptide pancretico).
- Basso livello sierico di vitamine liposolubili (A, D, E e K).

Perché l'elastasi è importante nella diagnosi di diabete di tipo 3c?

- Il diabete di tipo 3c si sviluppa in seguito a condizioni che danneggiano il pancreas, compromettendo sia la sua funzione endocrina (produzione di insulina) che esocrina (produzione di enzimi digestivi). La misurazione dell'elastasi fecale permette di identificare la disfunzione esocrina associata.
- **Ruolo specifico dell'elastasi**:
  - Prodotta dal pancreas esocrino: L'elastasi è un enzima digestivo secreto dal pancreas che aiuta nella digestione delle proteine.
  - Indicatore indiretto della funzione pancreatica: In condizioni normali, viene escreto nelle feci in quantità significative, senza subire una degradazione rilevante durante il transito intestinale.
  - Se i livelli di elastasi fecale sono bassi, questo indica insufficienza pancreatica esocrina (EPI).
- **Livelli di elastasi fecale nei pazienti con diabete tipo 3c:**
  - **Valori normali:** >200 µg/g di feci.
  - **Insufficienza moderata:** 100-200 µg/g di feci.
  - **Insufficienza grave:** <100 µg/g di feci.

Pathophysiology of type 3c diabetes

- Recognizing the role of pancreatic damage in the development of a patient's diabetes is vital to inform appropriate management plans.
- The production of **insulin is usually reduced** caused by β-cell dysfunction following pancreatic inflammation and fibrosis or by absolute β-cell loss
- **Pancreatic polypeptide upregulates insulin receptor expression in the liver**, and its loss can lead to **hepatic insulin resistance** an important physiological difference between diabetes of the exocrine pancreas and type 1 diabetes.
- **Glucagon** production from pancreatic α-cells is also **diminished**, which may explain the episodes of **severe hypoglycemia** that are reported in some patients
- Failure to recognize this altered physiology may result in suboptimal treatment.
- Insulinopenic patients with diabetes of the exocrine pancreas could be unfairly labeled as poorly compliant if they are misclassified as type 2 diabetes and show resistance to oral antihyperglycemic agents.
- Malabsorption secondary to pancreatic exocrine dysfunction is common, and pancreatic enzyme and vitamin D replacement is required to prevent malnutrition and osteoporotic bone disease

Una corretta diagnosi è importante per le possibili implicazioni terapeutiche

American Diabetes Association.

Diabetes Care. 2017;40(11):1486-1493. doi:10.2337/dc17-0542

Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study

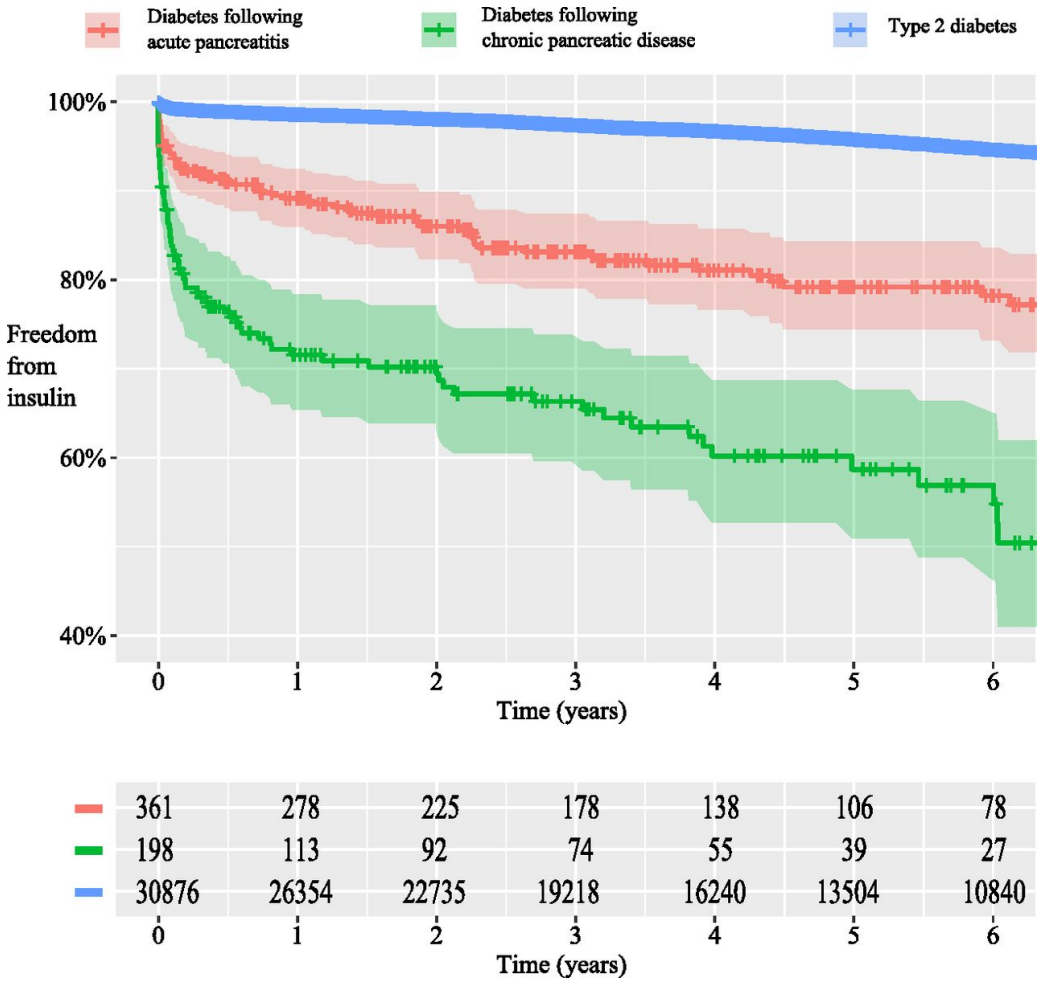
31,789 new diagnoses of adult-onset diabetes, 559 cases of pancreatic diabetes

PD associated with poor glycemic control and early initiation and higher frequency of insulin therapy compared with type 2 diabetes.

1 yr 1.4% vs 16.3%

5 yrs 4.1% vs 29.6% (20.9AP; 45.8CP)

OR 9.5 (P < 0.001)



Diabetes of the exocrine pancreas is frequently labeled type 2 diabetes but has **worse glycemic** control and a markedly **greater requirement for insulin**.

TERAPIA

INTERVENTI SULLO STILE DI VITA

Per tutti i pazienti affetti da diabete pancreatico sono fondamentali interventi sullo stile di vita (con rinforzo ad ogni visita):

- Perdita di peso nei soggetti obesi o in sovrappeso
- Esercizio quotidiano
- Eventuale terapia nutrizionale specifica
- Astenersi da alcol e fumo

IL DIABETE IN ITALIA

Popolazione generale: ~ 60.000.000

Diabete ignoto: ~ 1.000.000

Diabete noto: ~ 4.000.000

Tipo 1: *~ 200.000 (5%)*

LADA: *~ 200.000 (5%)*

Tipo 2: *~ 3.500.000 (87%)*

Secondario: *~ 50.000-100.00 (1.5-2.5%%)*

Monogenico: *~ 50.000-200.000*

DIABETE MONOGENICO
0.5-5% dei pazienti diagnosticati T2D
5-6% dei pazienti pediatrici
3% delle donne con GDM

Stima dall'Osservatorio ARNO Diabete CINECA-SID

Diabete monogenico: che fare?
Le tre domande del clinico

1. Come sospettarlo
2. Come diagnosticarlo
3. Come monitorarlo e trattarlo

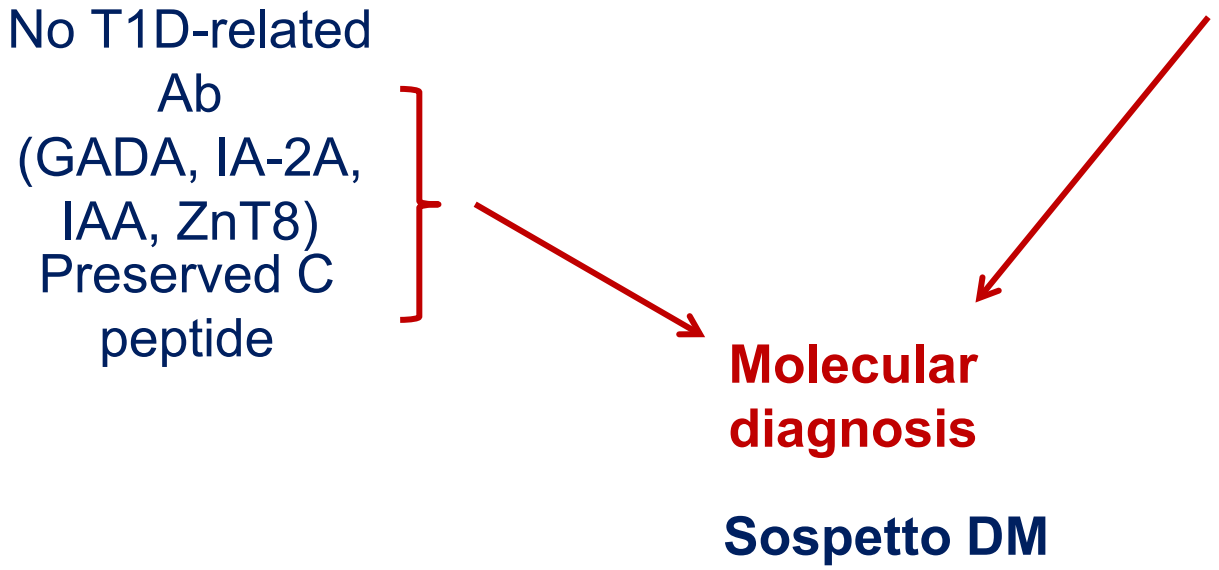
Come sospettare il diabete monogenico

T1D?

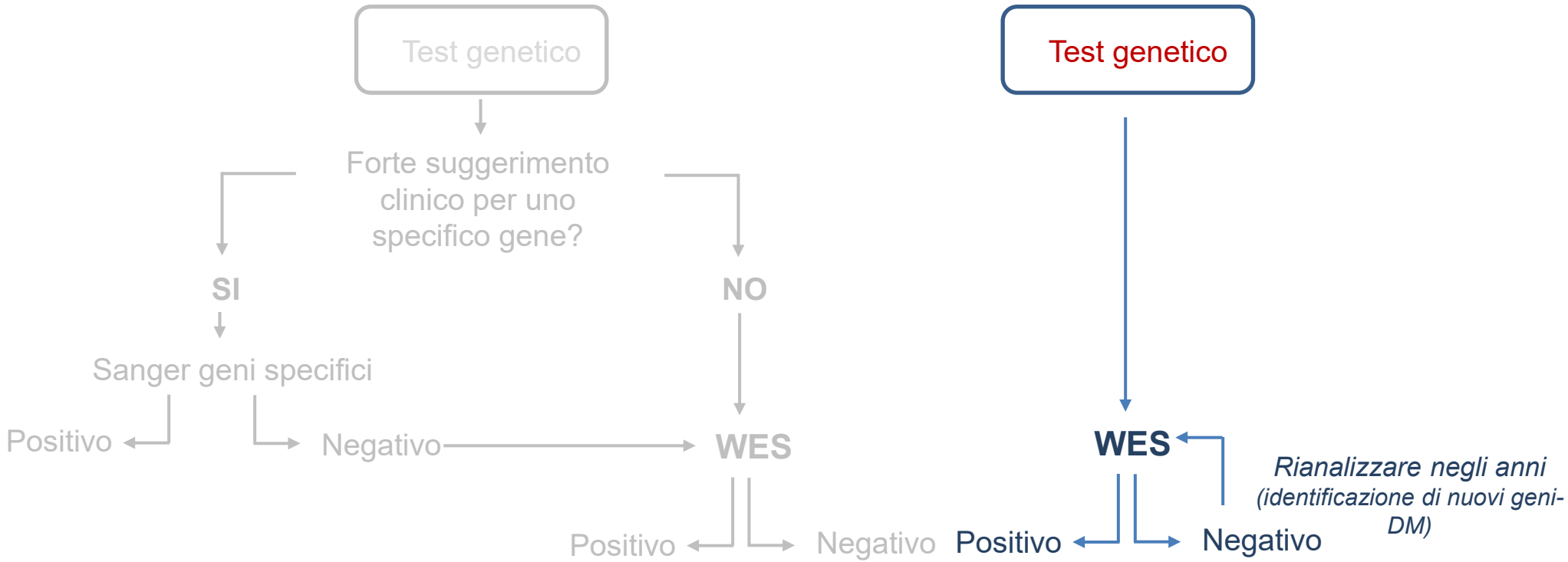
Family history of diabetes
No ketosis (modest hyperglycemia)
Extra-pancreatic features

T2D?

Early onset (<30yrs)
No obesity (no dyslipidemia)
Family history of diabetes
Extra-pancreatic features



Diagnosi molecolare del DM



Perchè è importante fare il test genetico diagnostico in caso di sospetto Doiabete Monogenico (DM)

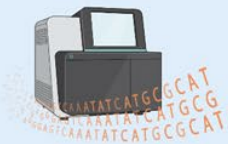
1. Pone diagnosi certa di DM (a differenza di quanto possa fare la clinica, soprattutto nei casi sporadici) e ne definisce l'endotipo
2. Permette di definire la prognosi e ottimizzare lo screening/prevenzione delle complicanze croniche
3. Permette di estendere lo screening ai familiari ancora asintomatici per identificare precocemente i soggetti affetti e quelli a rischio
4. Ma soprattutto, offre la possibilità di individualizzare il trattamento evitando, incongrue terapie

Precision Diagnostics

Neonatal Diabetes

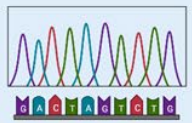
Gestational Diabetes

Early onset diabetes



Neonatal Diabetes Gene Panel

Monogenic Diabetes Gene Panel



e.g. *KCNJ11*
e.g. *GCK*
e.g. *HNF1A*

Precision Treatment

Neonatal Diabetes

KCNJ11
High dose sulfonylureas

Gestational Diabetes

GCK
pregnancy specific management informed by fetal genotype, with postpartum withdrawal of all glucose lowering therapy

Early onset diabetes

HNF1A
switch glucose lowering therapy to low dose sulfonylurea

Precision Prognostics

Neonatal Diabetes

KCNJ11
monitor for microvascular or macrovascular complications

Gestational Diabetes

GCK
no need for microvascular or macrovascular complication screening

Early onset diabetes

HNF1A
macrovascular risk treatment despite normal lipids

Gaps & Challenges

- Funding for genetic testing and integration of clinical decision support tools into the health care system is critical to support equitable access to precision medicine for monogenic diabetes.
- Large-scale unselected screening for monogenic diabetes is needed to capture the true variation in clinical picture, treatment response and prognostics.

Take home messages

Clinical applications of precision medicine is challenging in T2D because:

- Highly prevalent condition -> expensive testing unlikely to become practical
- Complex pathophysiology, changing over time

Prompt recognition of adult-onset autoimmune diabetes is a first step towards «precision diabetes»

Monogenic Diabetes needs to be searched and diagnosed. Prevalence higher than expected.

Simple clincal measures appear more useful to subclassify diabetes (c-peptide, e GFR, BMI, age at diagnosis, HbA1c at diagnosis.)

PRIN 2022 PNRR

PNRR

MISSIONE 6 - SALUTE

Funding from the European Union's under the program EU4Health (EU4H)