



American
Diabetes
Association®

82ND SCIENTIFIC
SESSIONS

HYBRID | NEW ORLEANS | JUNE 3-7, 2022

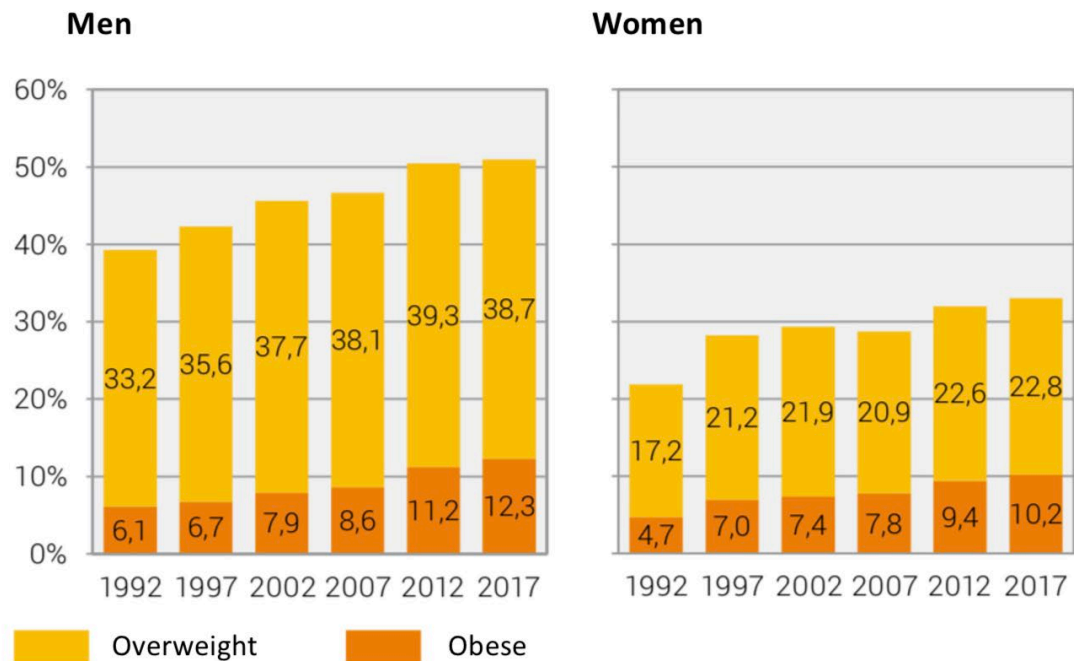
20th Post-ADA Symposium, Sept 1st 2022

Epidemiology & Economics

Katja Leitner - Beat Müller



Overweight and obese inhabitants in Switzerland > 15y



Quelle: BFS – Schweizerische Gesundheitsbefragung (SGB)

Diabetes – a heavy burden for the individual AND society



2695 CHF BUT only direct costs

Medication 500 CHF

+ Blood glucose measurement: 200 – 940 CHF

+ Outpatient care 770 - 1000 CHF

• Myocardial Infarction **5138 – 12.500 CHF**

• Amputation **12,818 – 20.512 CHF**

• End-stage renal disease

23.629 – 32.738 CHF

How can the avalanche of costs be stopped? **Precision Medicine?**

How to choose the right therapy option?

HbA1c = 6.8 %

Metformin + ?

Is there a way to predict disease course and outcomes?



Precision medicine: disease prevention and treatment on behalf of people's individual variations in genes, environment and lifestyle

Example pathways

Beta cell function

Insulin action (liver)

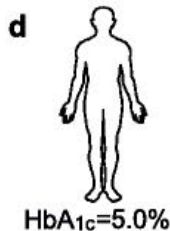
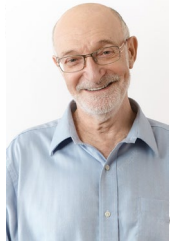
Insulin action (muscle)

Glucagon secretion/action

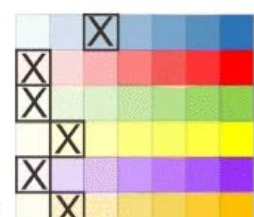
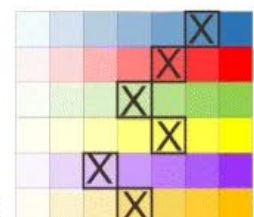
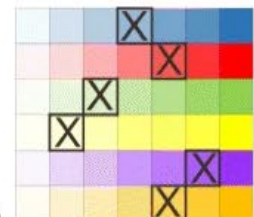
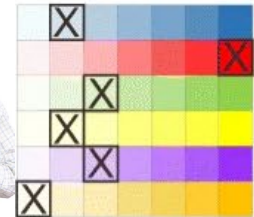
Incretin secretion/action

Adipose distribution

Diabetes component pathways



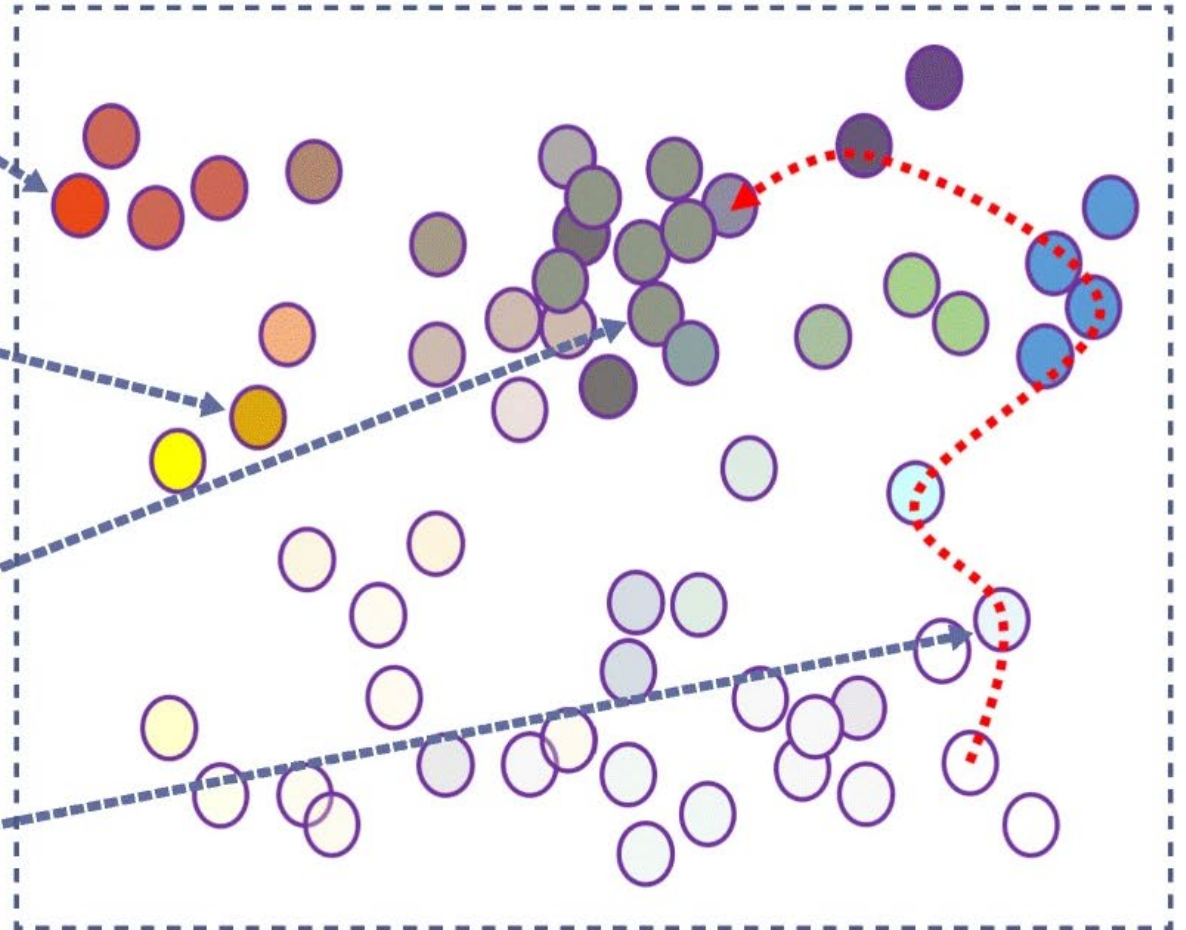
Individual

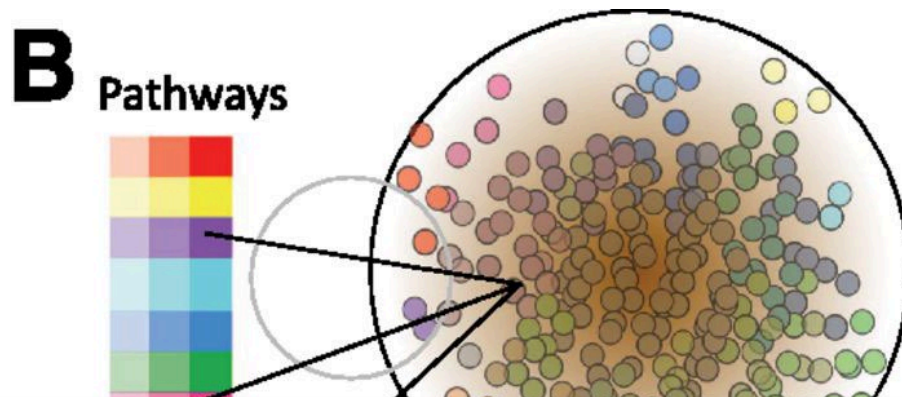
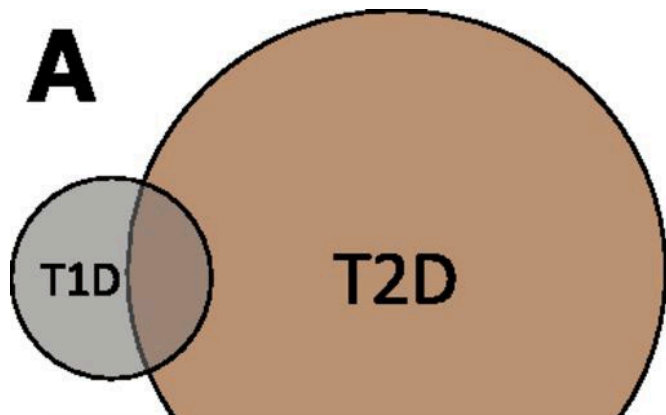


HbA_{1c}=5.0%

Low → High

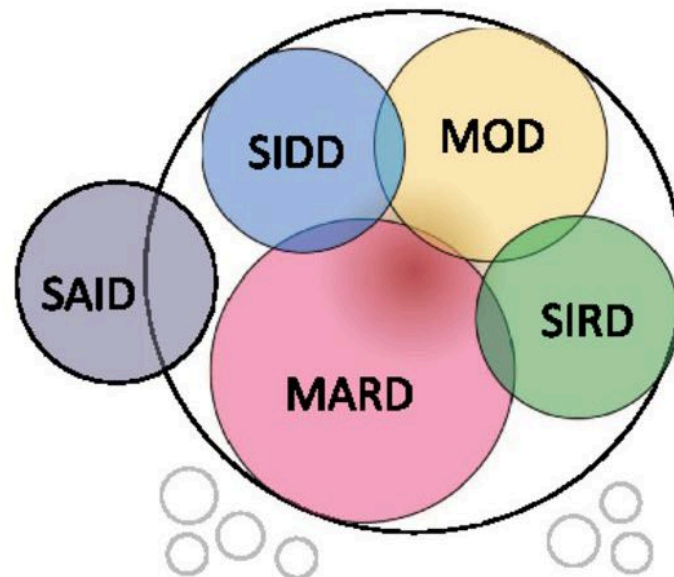
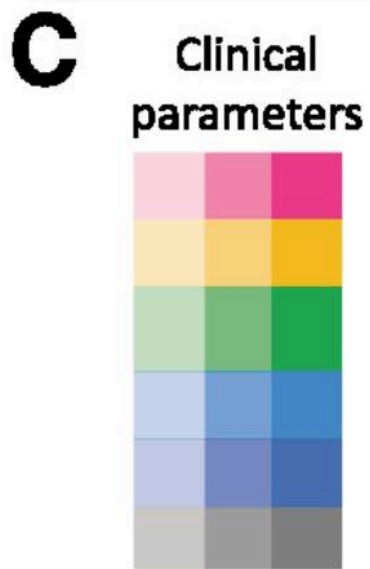
Type 2 diabetes risk





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*, Mozghan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spéjel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamajja Tuomi, Anders H Rosengren, Leif Groop*



T1D
LADA

GADA



6%

SAID = Severe Autoimmune Diabetes
GADA, low insulin secretion, poor metabolic control

SIDD = Severe Insulin Deficient Diabetes
Low insulin secretion, poor metabolic control,



18%

SIRD = Severe Insulin Resistant Diabetes
Insulin resistance, obesity, late onset,

HbA1c
HOMA-B
HOMA-IR
BMI
Age



15%

MOD = Mild Obesity-Related Diabetes
Obesity, early onset



22%

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



39%

T2D

All New Diabetics in Scania Cohort (ANDIS) (n=8980)

Scania Diabetes Registry(SDR) (n=1466)

All New Diabetics in Uppsala (ANDIU) (n=844)

Diabetes Registry Vaasa (DIREVA) (n=3485)

Malmö Diet and Cancer Cardiovascular Arm (MDC-CVA): (n=3300)

Clusters of subtypes based on 6 variables

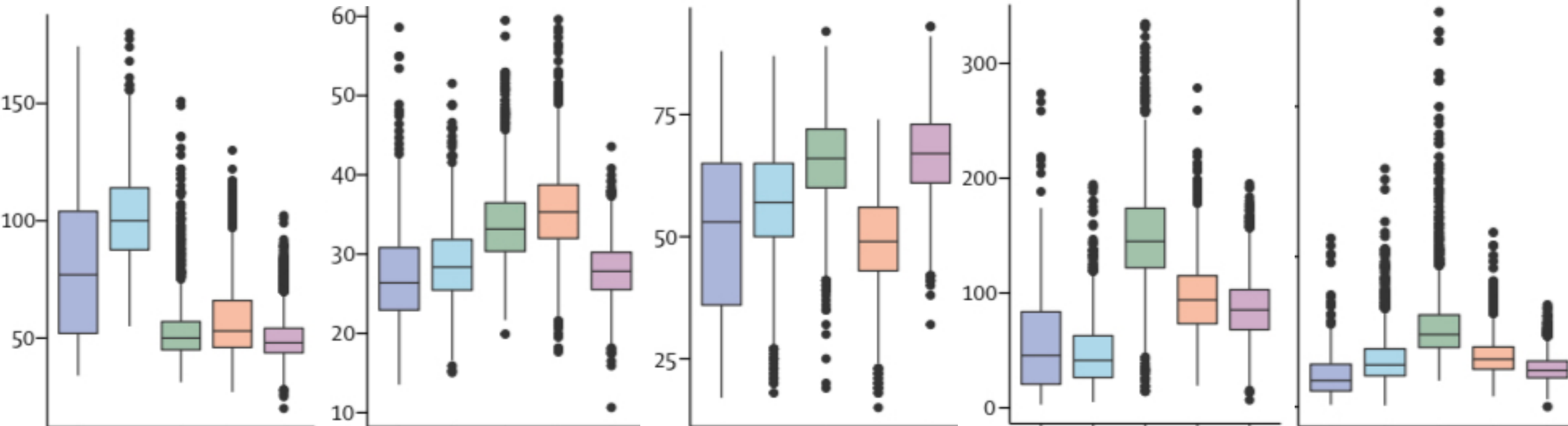
HbA1c

BMI

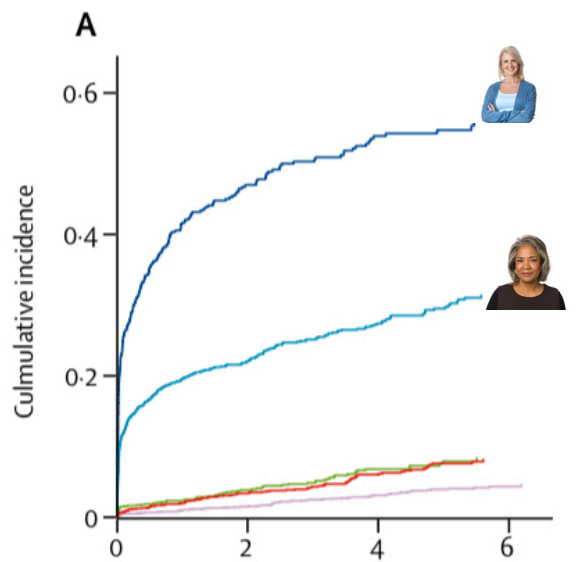
Age at onset

Beta cell Function

Insulin Resistance



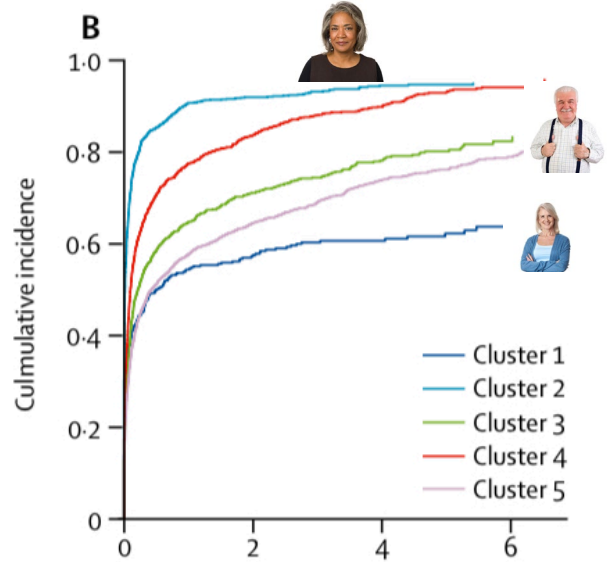
Time to sustained insulin use



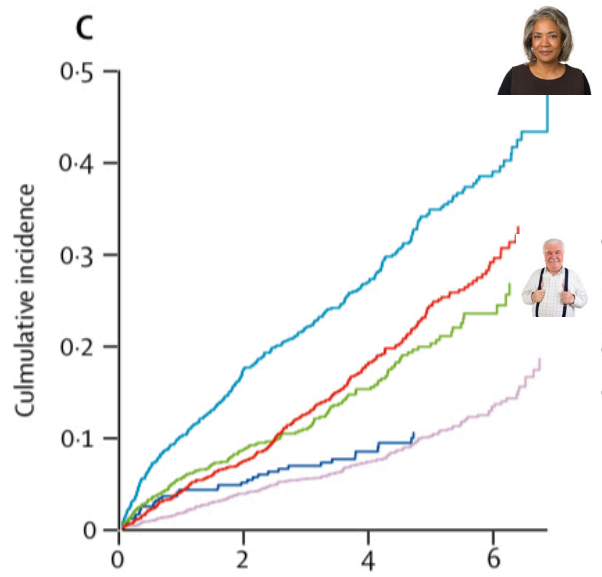
Number at risk

Cluster 1	424	140	65	16
Cluster 2	1158	569	258	58
Cluster 3	997	592	258	49
Cluster 4	1407	886	404	86
Cluster 5	2463	1584	766	181

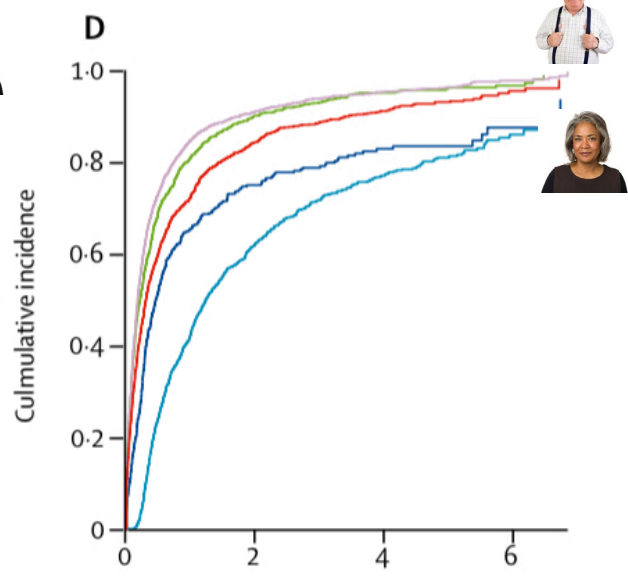
Time to treatment with metformin



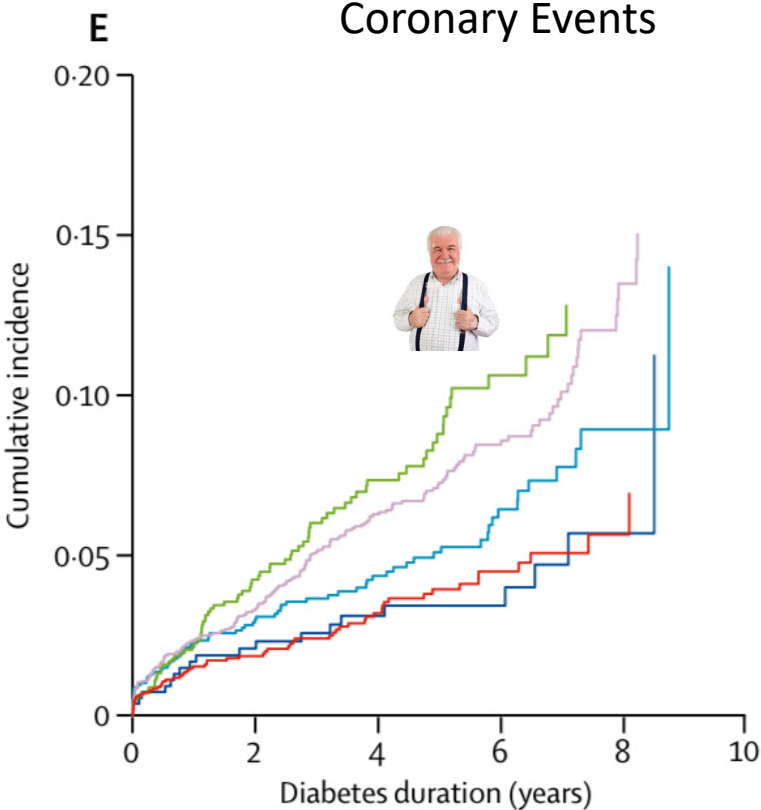
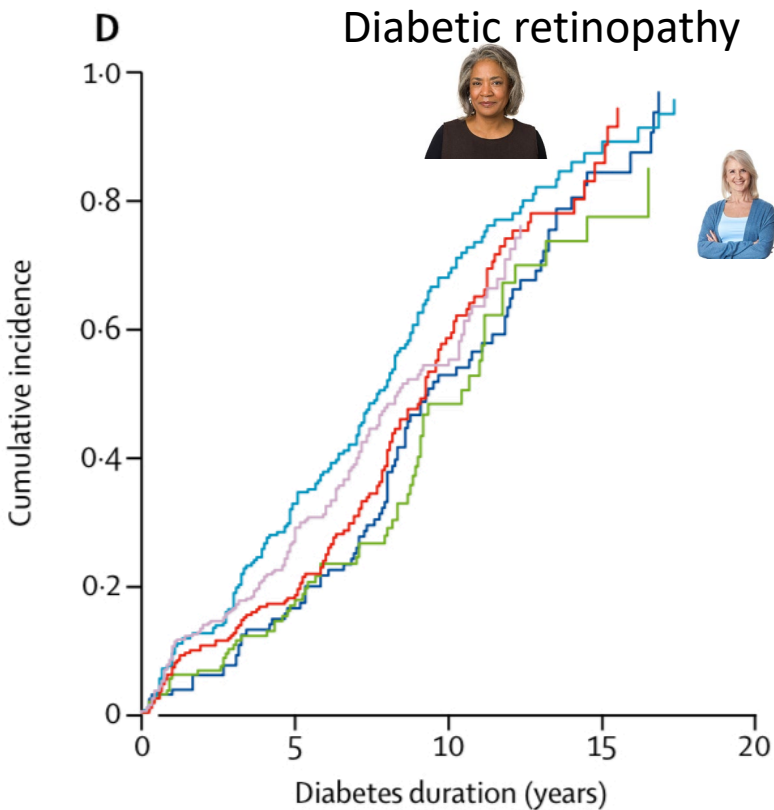
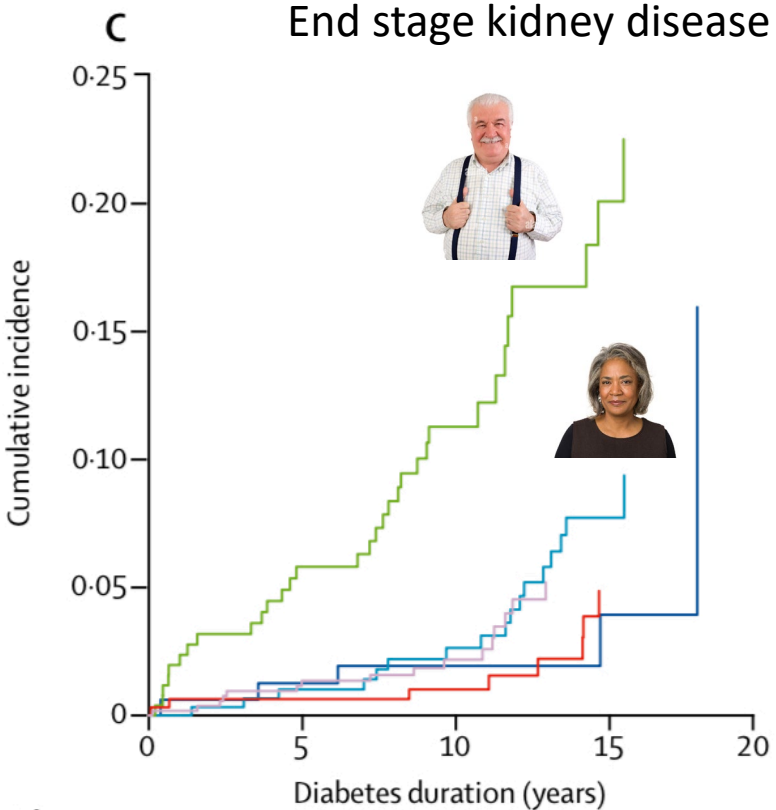
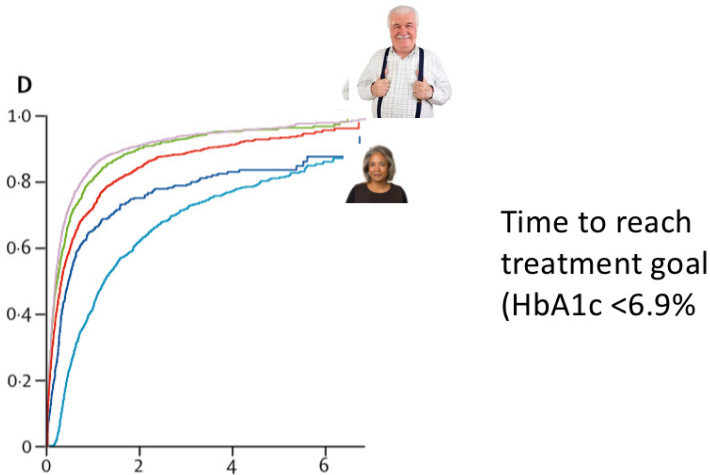
Time to treatment with oral medication other than metformin



Time to reach treatment goal (HbA1c <6.9%)



Clusters show different risk for complications



Clinical relevance has been assessed in multiple cohorts

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*, Mazhgan 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

➤ Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study *Lancet Diabetes Endocrinol* 2019; 7: 684-94

➤ 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 *Lancet Diabetes Endocrinol* 2019; 7: 442-51

➤ Novel subgroups of patients with adult-onset diabetes in Chinese and US populations. *Lancet Diabetes Endocrinol*. 2019 Jan;7(1):9-11

Validation of distinct type 2 diabetes clusters and their association with diabetes complications in the DEVOTE, LEADER and SUSTAIN-6 cardiovascular outcomes trials

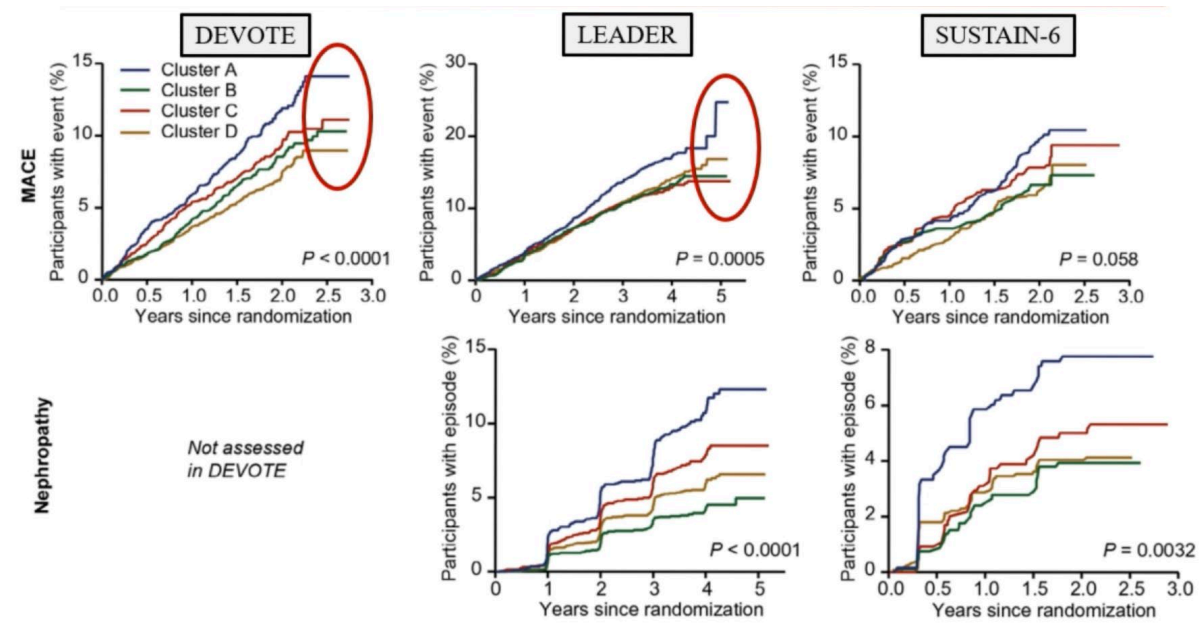
Anna R. Kahkoska PhD¹ | Milan S. Geybels PhD² | Klara R. Klein MD¹ | Frederik F. Kreiner PhD² | Nikolaus Marx MD³ | Michael A. Nauck MD⁴ | Richard E. Pratley MD⁵ | Benjamin O. Wolthers MD² | John B. Buse MD¹

Diabetes Obes Metab. 2020;22:1537–1547.

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

Marie Pigeyre^{1,2,3} | Sibylle Hess⁴ | Maria F. Gomez⁵ | Olof Asplund^{6,7} | Leif Groop^{6,7} | Guillaume Paré^{1,2,8,9} | Hertzfel Gerstein^{1,2,3,9}

Diabetologia (2022) 65:206–215

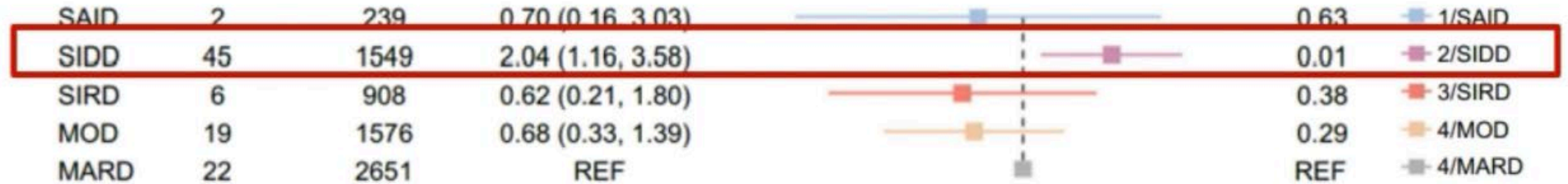


Validation of Diabetes Subtypes in Multi-ethnic Cohorts

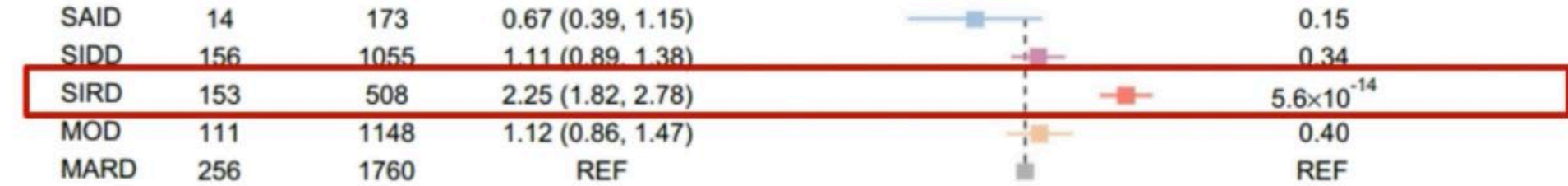
ORIGIN Trial

1/SAID 2/SIDD 3/SIRD 4/MOD 4/MARD

Retinopathy



CKD 3B



Macroalbuminuria



0.1 0.5 1.0 2.0 3.0 5.0
HR (95% CI)

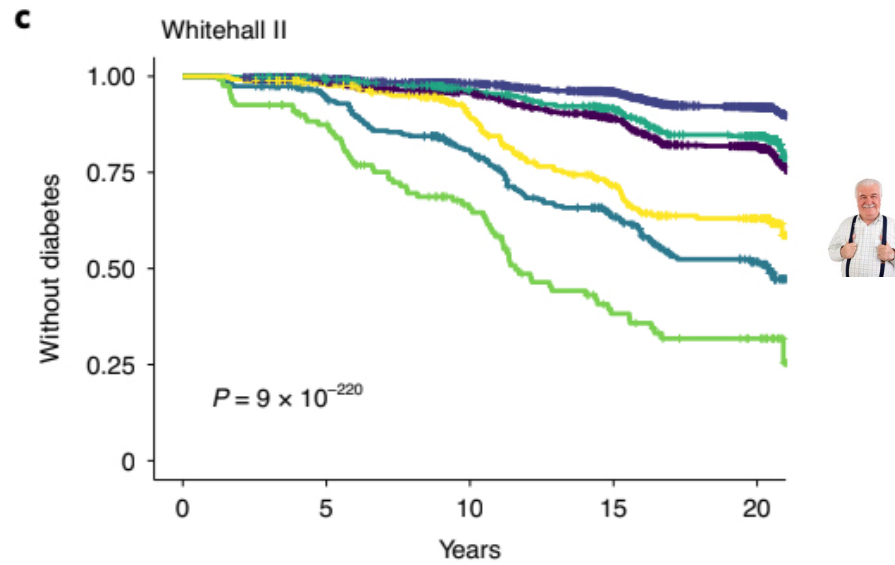
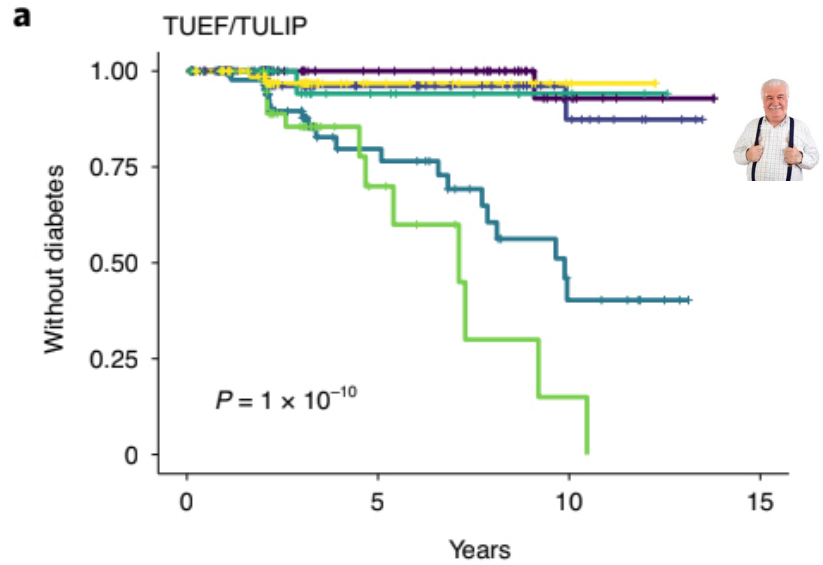
Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes

Robert Wagner^{1,2,3}✉, Martin Heni^{1,2,3,4}, Adam G. Tabák^{5,6,7}, Jürgen Machann^{1,2,8}, Fritz Schick^{2,8}, Elko Randrianarisoa^{1,2}, Martin Hrabě de Angelis^{2,9,10}, Andreas L. Birkenfeld^{1,2,3}, Norbert Stefan^{1,2,3,11}, Andreas Peter^{1,2,4}, Hans-Ulrich Häring^{1,2} and Andreas Fritsche^{1,2,3}

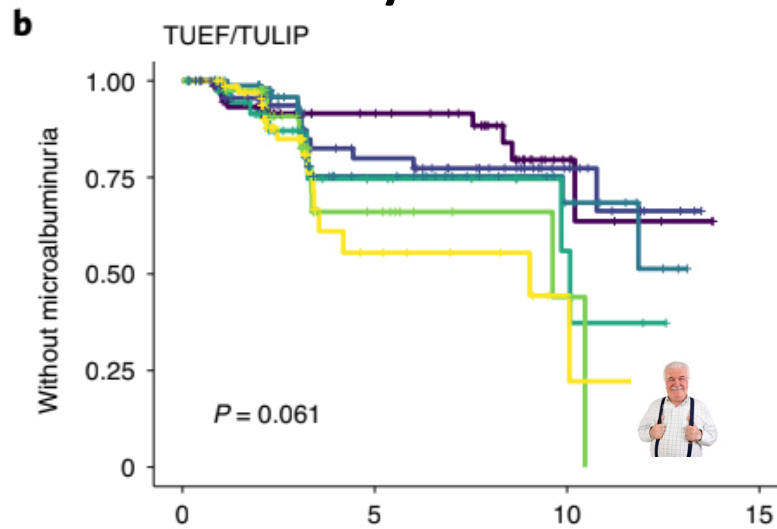
- Estimates of Insulin secretion/resistance (OGTT)
- Subcutaneous/visceral Body fat (MRI)
- Hepatic Fat Content (H-MR Spectroscopy)
- Genetic Risk (Polygenic T2D Risk Score)
- HDL



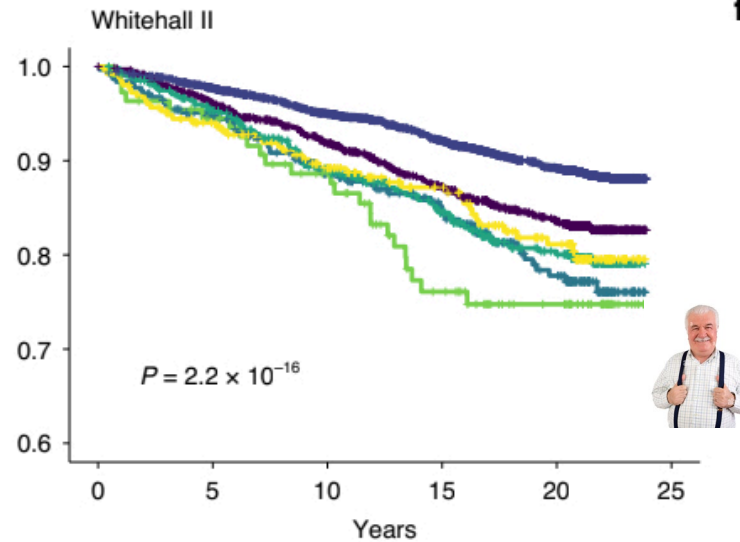
Different time to onset of Diabetes



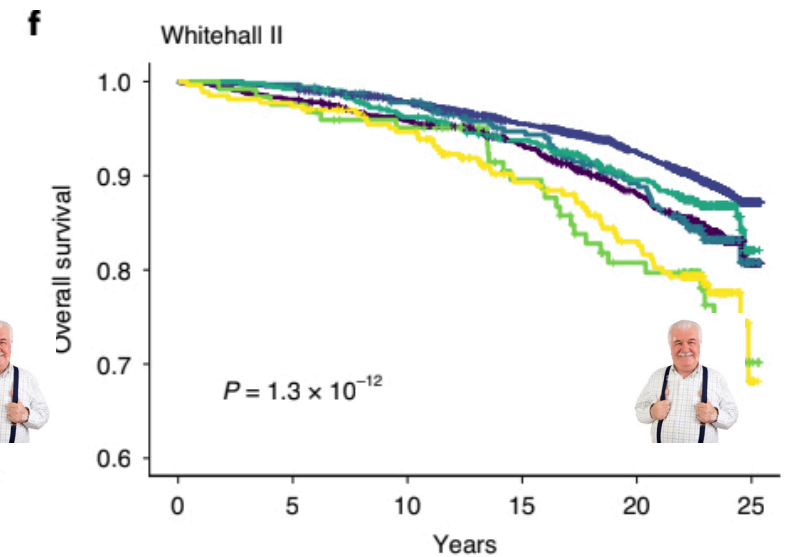
Kidney Disease



Coronary Heart Disease



Overall Survival



Challenge: matching the right patient with the right therapy at the right time

Prevent comorbidities
Prevent adverse events from pharmacotherapy
Delay in onset of diabetes and comorbidities
Decrease cost of care



Treatment options are plausible to have different effects in people with different pathophysiology

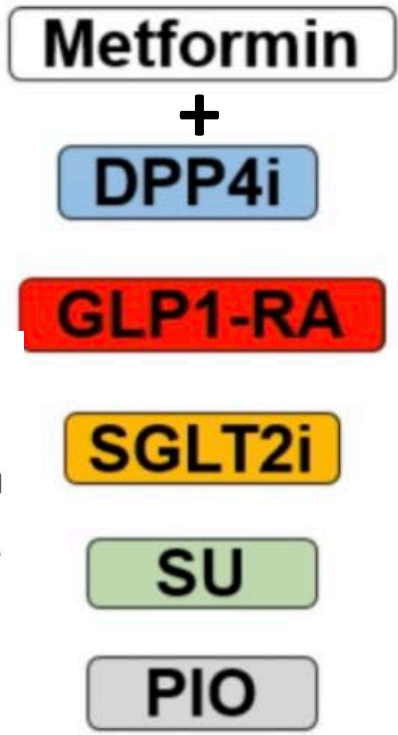
Anthony



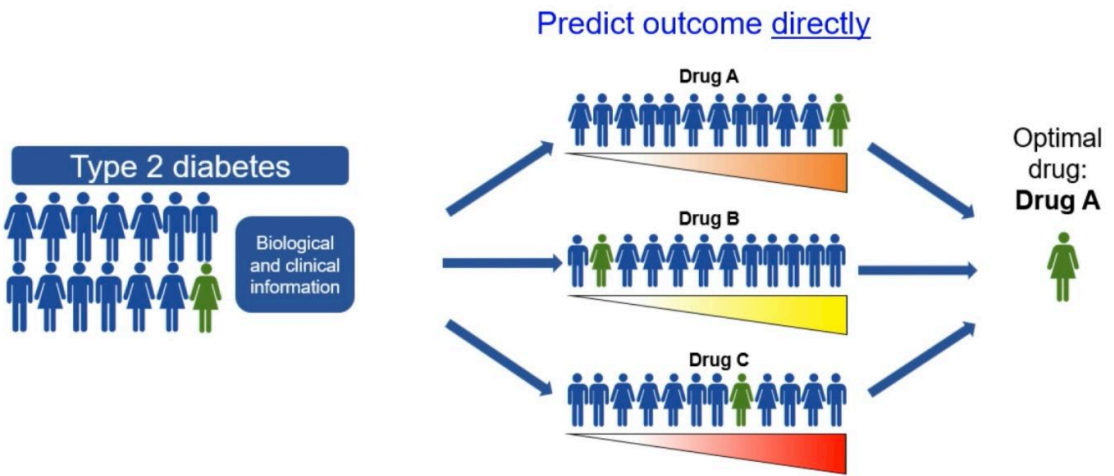
Barbara



Carl

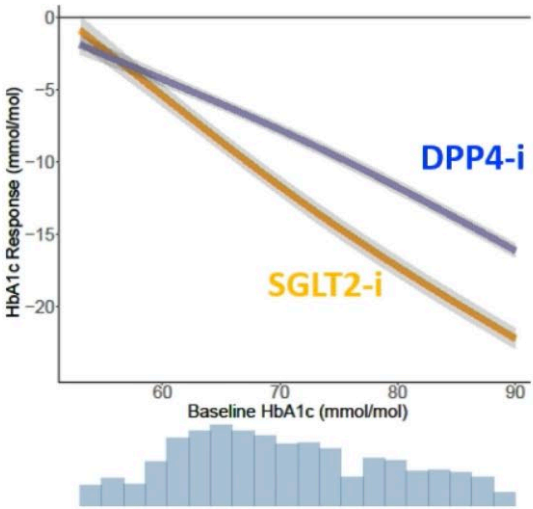


- Primary mechanism of action**
- Decreased hepatic glucose production
 - Increased insulin secretion, reduced glucagon secretion
 - Increased insulin secretion, reduced glucagon secretion, improved satiety
 - Lower glucose reabsorption in the kidney
 - Increased insulin secretion
 - Increased insulin sensitivity

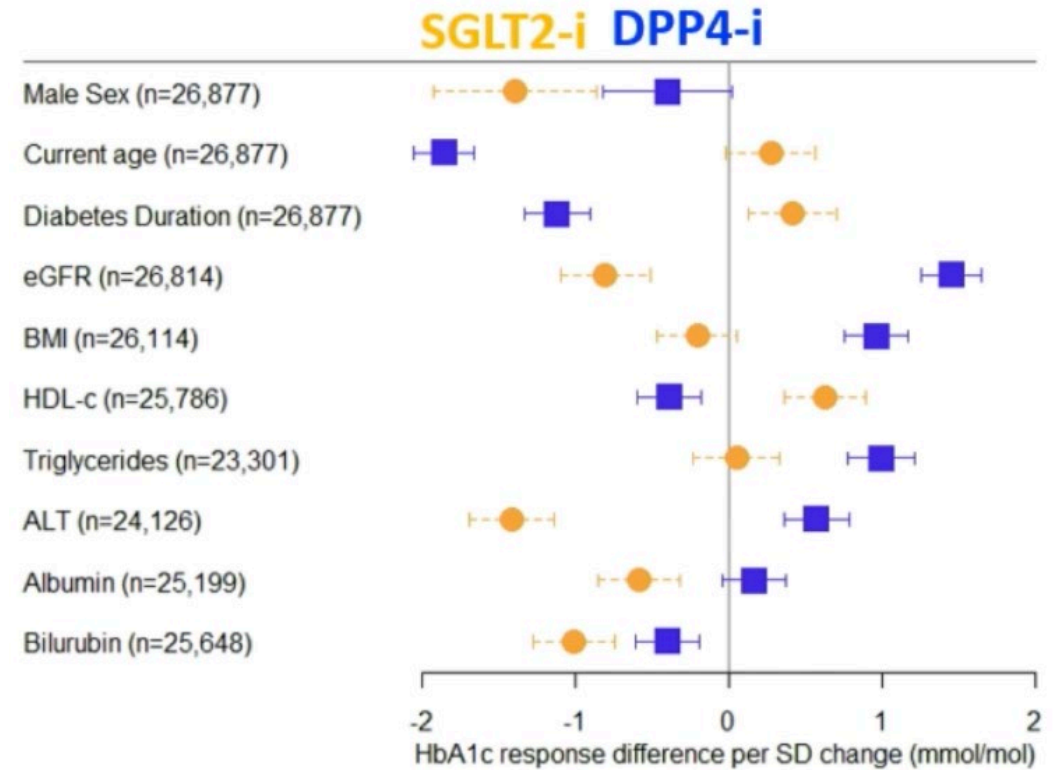
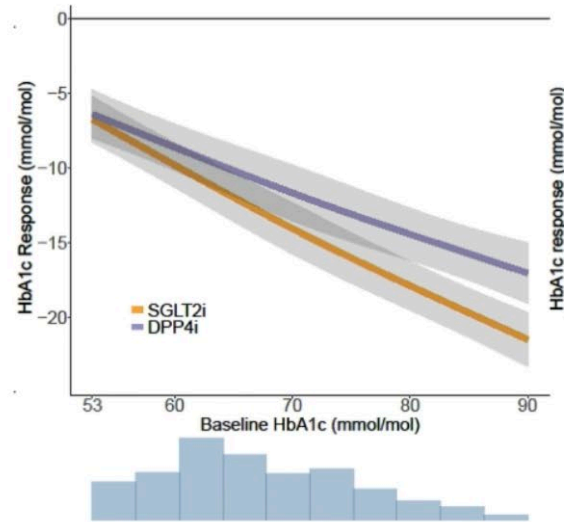


SGLT2i vs. DPP4i: other clinical features associated with HbA1c response

Routine data (n=26,877)



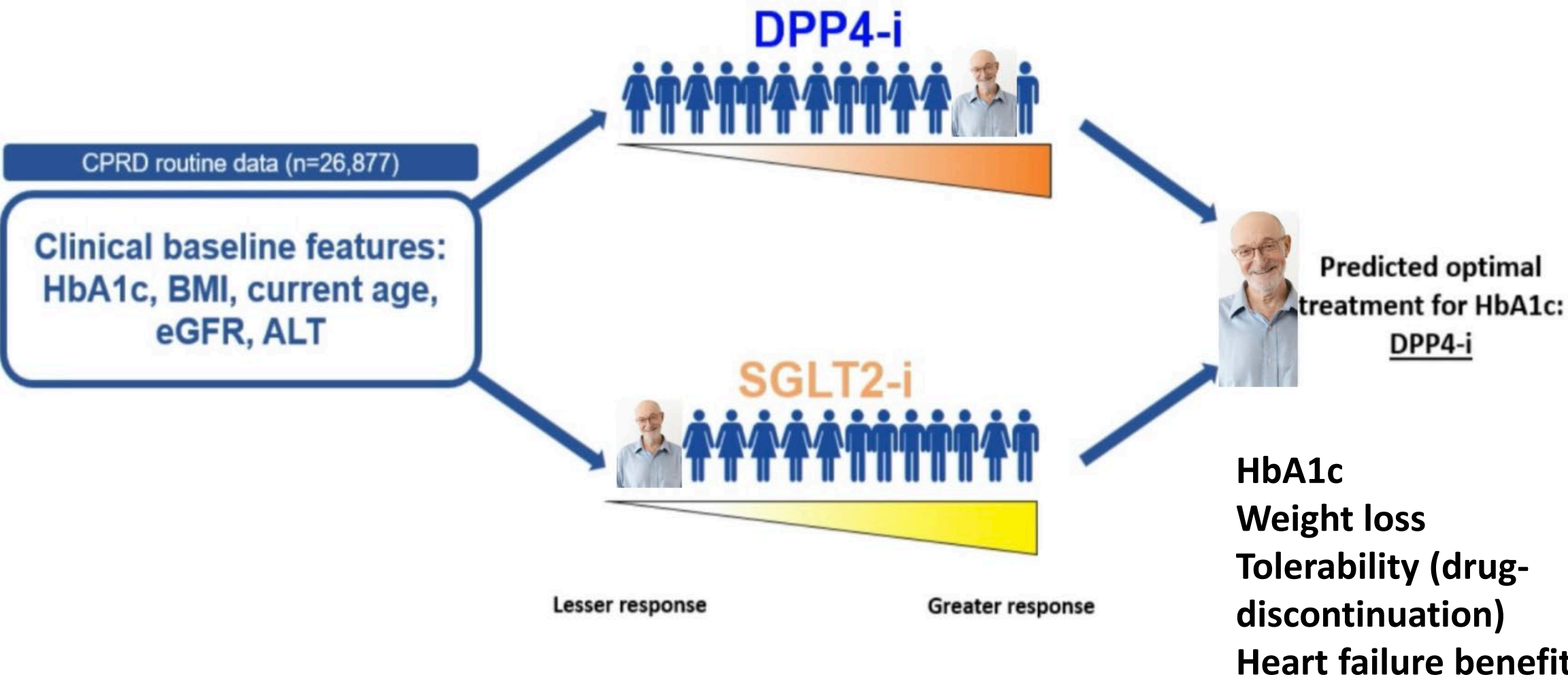
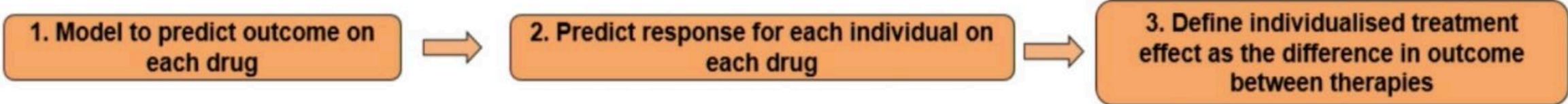
Trial data (n=1,755)



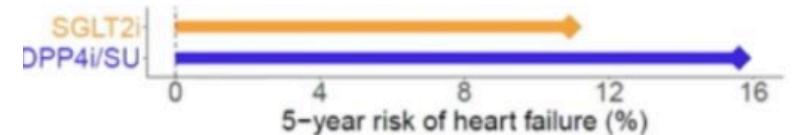
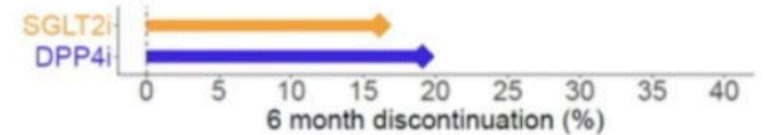
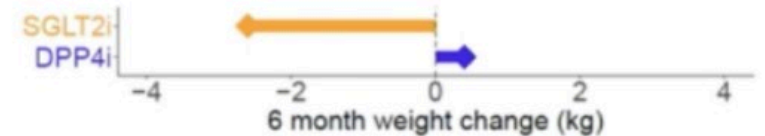
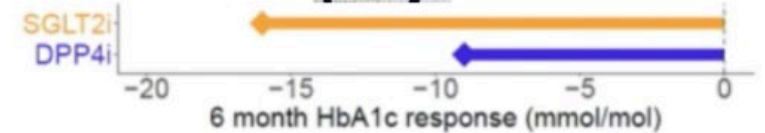
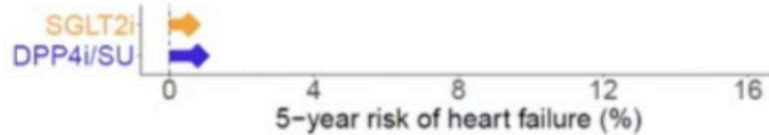
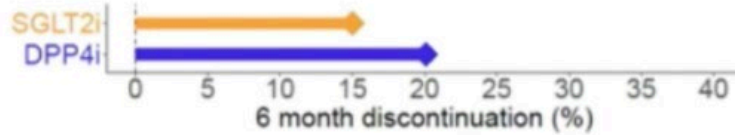
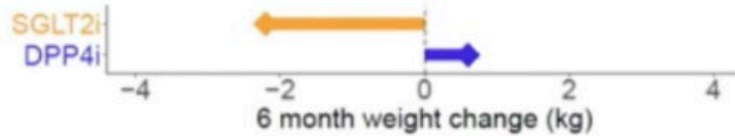
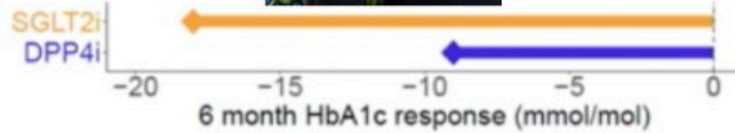
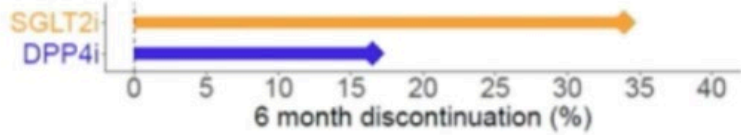
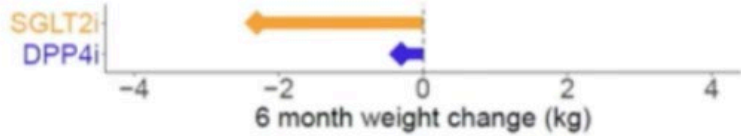
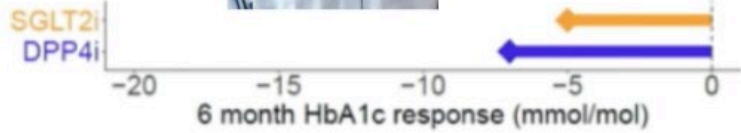
higher 'predictor' = **greater** response higher 'predictor' = **lesser** response

¹Dennis, Jones et al. Diabetes Care

²Dennis, Jones, Shields et al. medrxiv 10.1101/2021.11.11.21265959



The future of precision medicine?



MARD

no complications?



SGLT2 + Metformin: 810 CHF

vs.

DPP4+Metformin: 360 CHF

**Risk for comorbidities: low
-> less frequent follow ups**



SGLT2 earlier?

SIRD

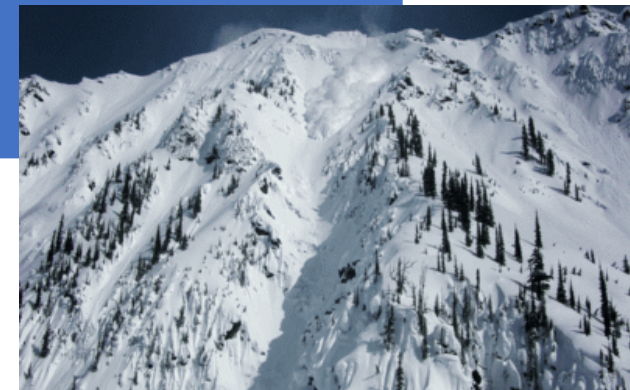
Nephropathy
(Ahqvist 2019, Dennis 2019, Tanabe 2020, Pigeyre 2022)

?Coronary events
(Pigeyre 2022)

End-stage renal disease €32,738.14 – €23,629.17



Can precision medicine stop the avalanche?



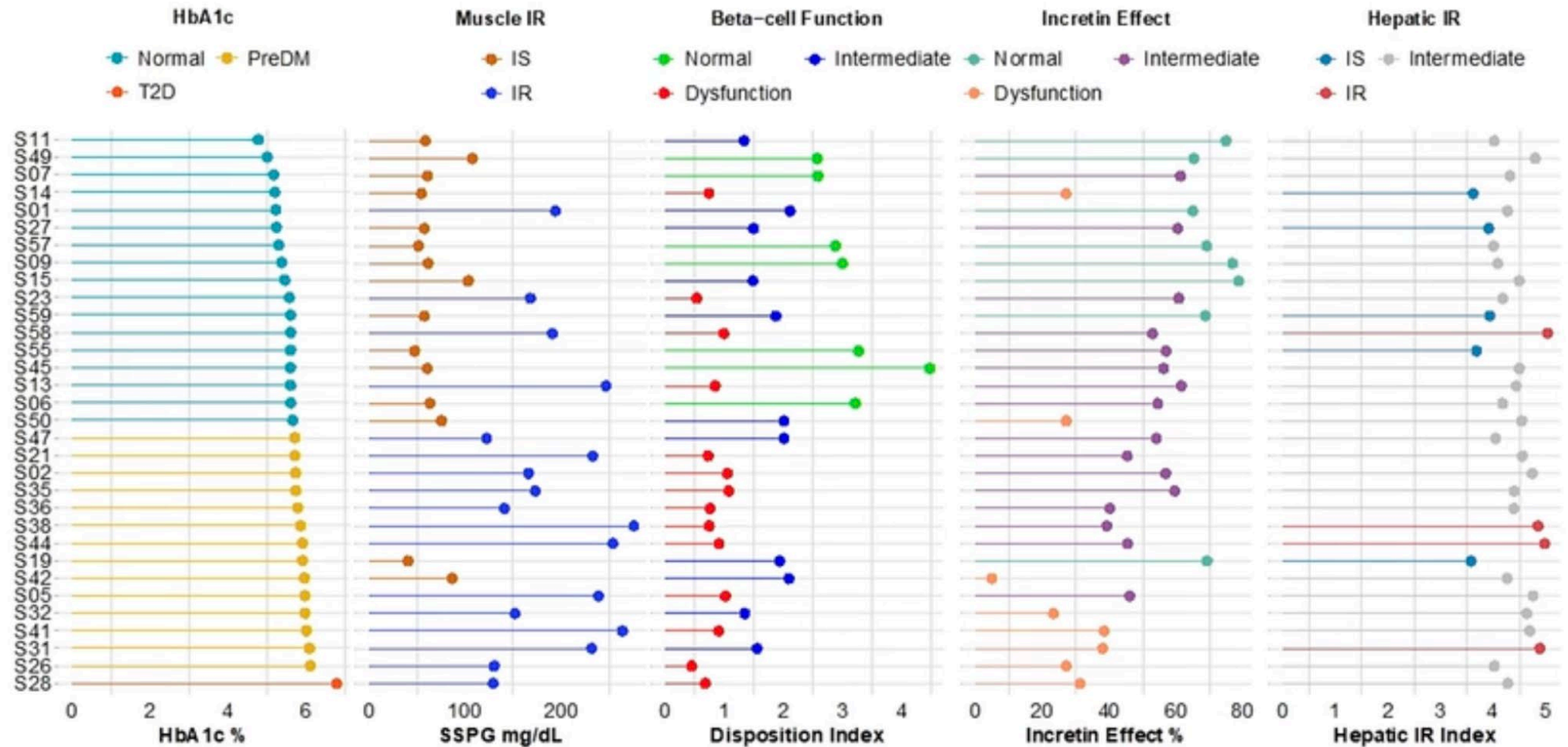
- Data suggests that clustering is better for predictions than glucose monitoring alone
- Goal: Optimize treatment decisions **BEFORE the damage is done**
- Wishful thinking until RCTs follow
- Open questions need to be answered



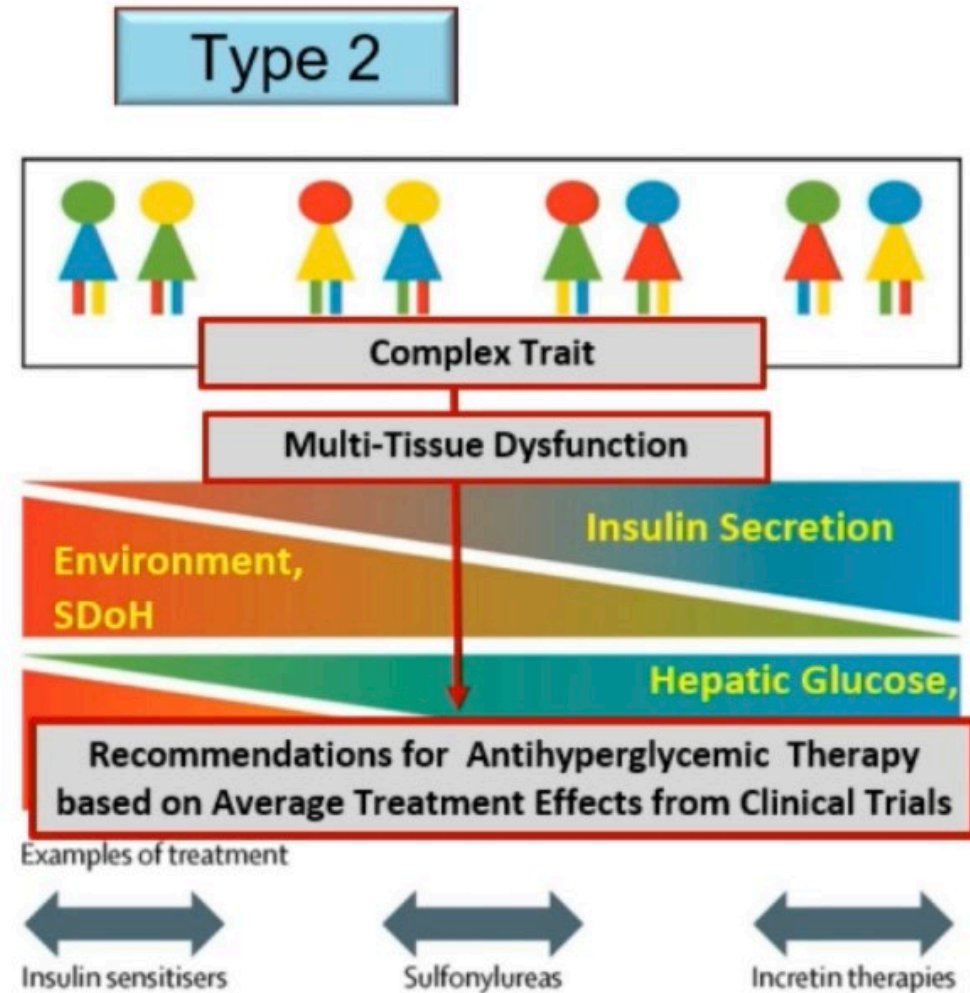
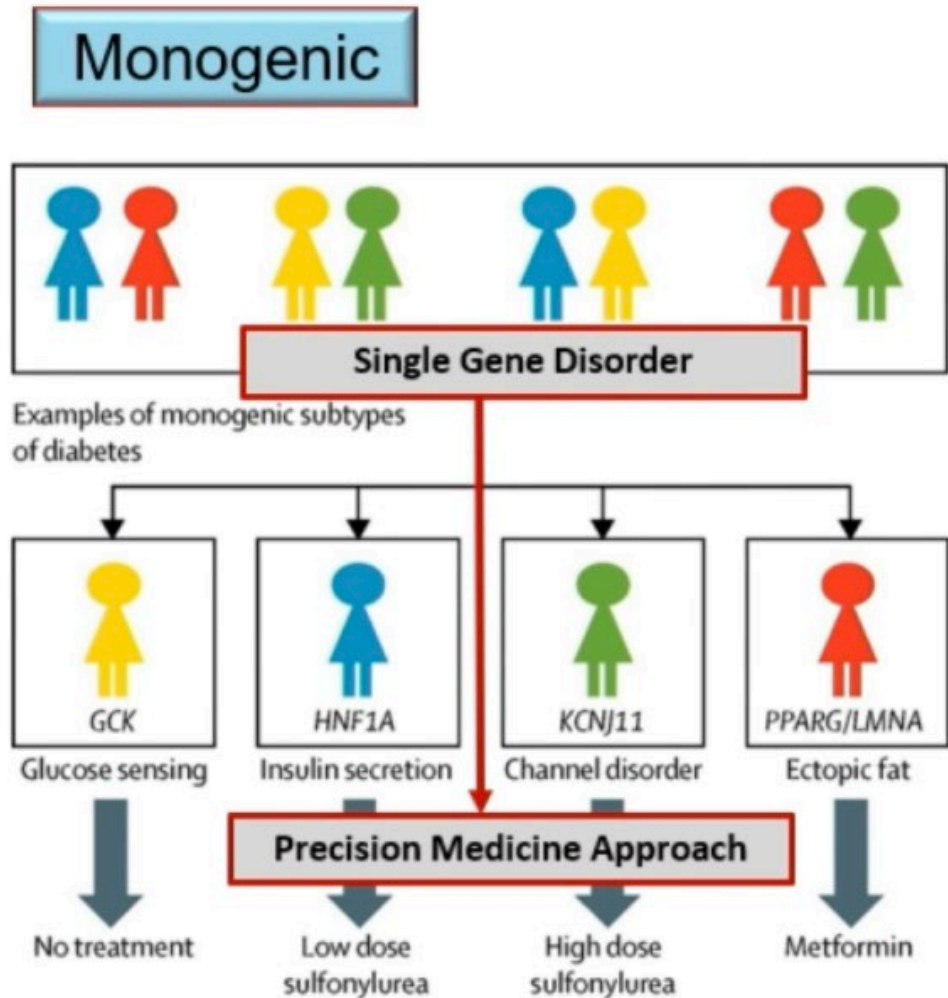


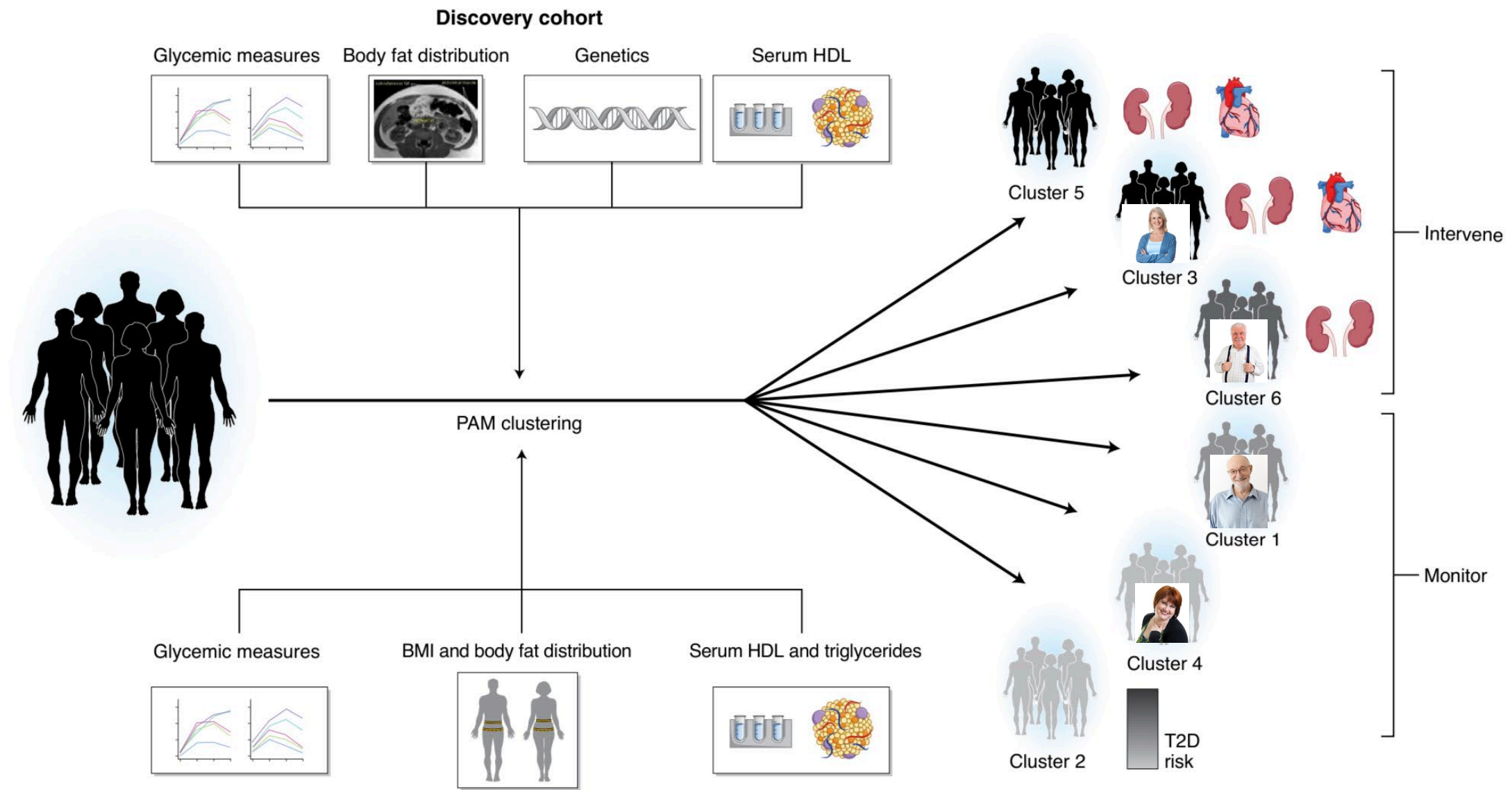
Thank you for
your attention

Heterogeneous responses to metabolic testing



Precision Medicine in Diabetology?





“I expect there are about 12 genes involved [in diabetes], and that all of them will be discovered in the next two years”

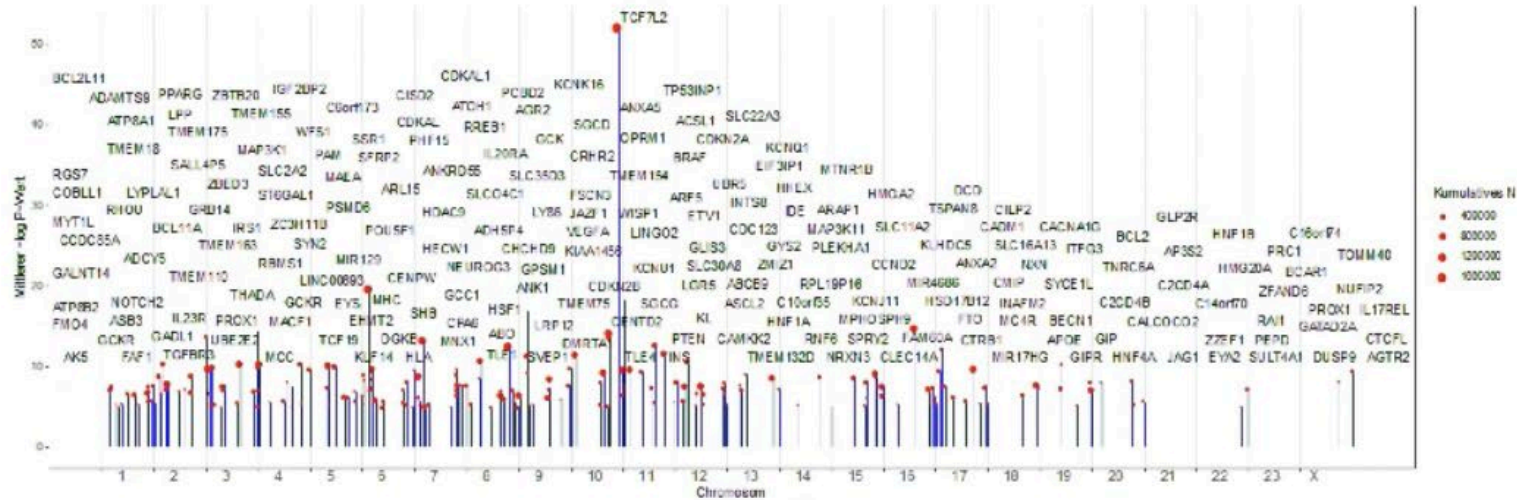


Francis Collins, 2006, Director, NIH

“I expect there are about 12 genes involved [in diabetes], and that all of them will be discovered in the next two years”



Francis Collins, 2006, Director, NIH



Wagner & Staiger, 2019; Mahajan et al, Nature Genetics, 2022

T2D-related genetic variants can be assigned to pathomechanisms

