Unlocking the Potential of Menin Inhibition

Icovamenib and a Look into the Future of Diabetes Management

Juan Pablo Frías, MD
Chief Medical Officer
Biomea Fusion, Inc.

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University of Toronto

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Professor of Medicine
Joslin Clinic, Harvard Medical School

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Alice YY Cheng, MD, FRCPC

- Endocrinologist and Associate Professor of Medicine, University of Toronto
- Trillium Health Partners and Unity Health Toronto
- Completed her medical education at the University of Toronto in 1998 and has since become a leading expert in diabetes care
- Involved with the development of the Diabetes Canada clinical practice guidelines since 2003, serving as Chair for the 2013 version
- Past-Chair of the Professional Section of Diabetes Canada
- Her contributions have earned her prestigious awards, including the Charles H. Best Award and the Gerald S. Wong Service Award from Diabetes Canada
- In addition to her clinical work, served as the Chair of the 2023-24 Scientific Planning Committee for the American Diabetes Association (ADA) Scientific Sessions, Co-host of podcast series "Diabetes Care on Air" and Associate Editor for the journal, Diabetes Care

Disclosures

- **Advisory panel / consulting**: Abbott, Bayer, Biomea Fusion, Boehringer Ingelheim, Dexcom, Eisai, Eli Lilly, Insulet, HLS Therapeutics, Novo Nordisk, Sanofi, Vertex
- **Speaker or CME development**: Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, GSK, HLS Therapeutics, Medtronic, Novo Nordisk, Pfizer, Sanofi
- **Clinical trial:** Sanofi, Novo Nordisk, Applied Therapeutics

Rohit N. Kulkarni, MD, PhD

- Physician scientist and diabetes researcher
- Professor of Medicine at Harvard Medical School; Diabetes Research and Wellness Foundation Chair
- Co-Head of the Section on Islet and Regenerative Biology at the Joslin Diabetes Center, Principle Faculty of the Harvard Stem Cell Institute and Associate Member of the Broad Institute
- Research focuses on pathways in islet cell biology that are critical to understand the pathophysiology of diabetes
- Received numerous accolades, including the Ernst Oppenheimer Award (Endocrine Society), the Albert Renold Prize (European Association for Study of Diabetes) and Paul E. Lacy Medal (Midwest Islet Consortium)
- Elected Fellow of the American Society for Clinical Investigation, the Association of American Physicians, and the American Association for the Advancement of Science

Disclosures

- Scientific Advisory Board, Biomea Fusion
- Scientific Advisory Board, Novo Nordisk
- Scientific Advisory Board, REDD Pharmaceuticals

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Icovamenib and a Look into the Future of Diabetes Management

7:00 - 7:05	**Introduction to Biomea Fusion and Icovamenib**	**Juan P. Frías, MD**
7:05 – 7:20	**One Size Does Not Fit All: Subtypes of Type 2 Diabetes**	**Alice YY Cheng, MD, FRCPC**
7:20 – 7:35	**Menin Inhibition and Beta-Cell Biology**	**Rohit Kulkarni, MD, PhD**
7:35 – 7:45	**Q&A**	

Introduction to Biomea Fusion and Icovamenib

Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes
Biomea Fusion

biomea FUSION™ | We Aim to Cure™

A long history of developing successful drugs - together

Thomas Butler
Chairman & CEO

biomea FUSION™
Co-Founder

The FUSION™ SYSTEM
icovamenib*
Co-Inventor

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Veklury® remdesivir 100 MG FOR INJECTION
Co-Inventor

Ramses Erdtmann
President & COO

biomea FUSION™
Co-Founder

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Juan Frías, M.D.
Chief Medical Officer

once weekly mounjaro® (tirzepatide) injection 0.5 mL
2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

once weekly trulicity® (dulaglutide) injection 0.5 mL
0.75 mg | 1.5 mg | 3.0 mg | 4.5 mg

OZEMPIC® semaglutide injection 0.5 mg, 1 mg, 2 mg

Byetta® (exenatide) injection

ONCE-WEEKLY wegovy® semaglutide injection 2.4 mg

Januvia® sitagliptin

Invokana® (canagliflozin) tablets

Jardiance® (empagliflozin) tablets 10 mg/25 mg

farxiga® (dapagliflozin) 5 mg & 10 mg tablets

Naomi Cretcher
Chief of People

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Heow Tan
Chief Technical & Quality Officer

ZADAXIN®

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

PLENAXIS®

HylatopicPlus® Cream

Steve Morris, M.D.
Chief Development Officer

XALKORI® 250 MG CAPSULES CRIZOTINIB

ZYKADIA® ceritinib 150 mg tablets

LORBRENA® LORLATINIB | 100 mg tablets

ALECENSA® alectinib 150 mg capsules

ALUNBRIG™ BRIGATINIB 30mg TABLETS

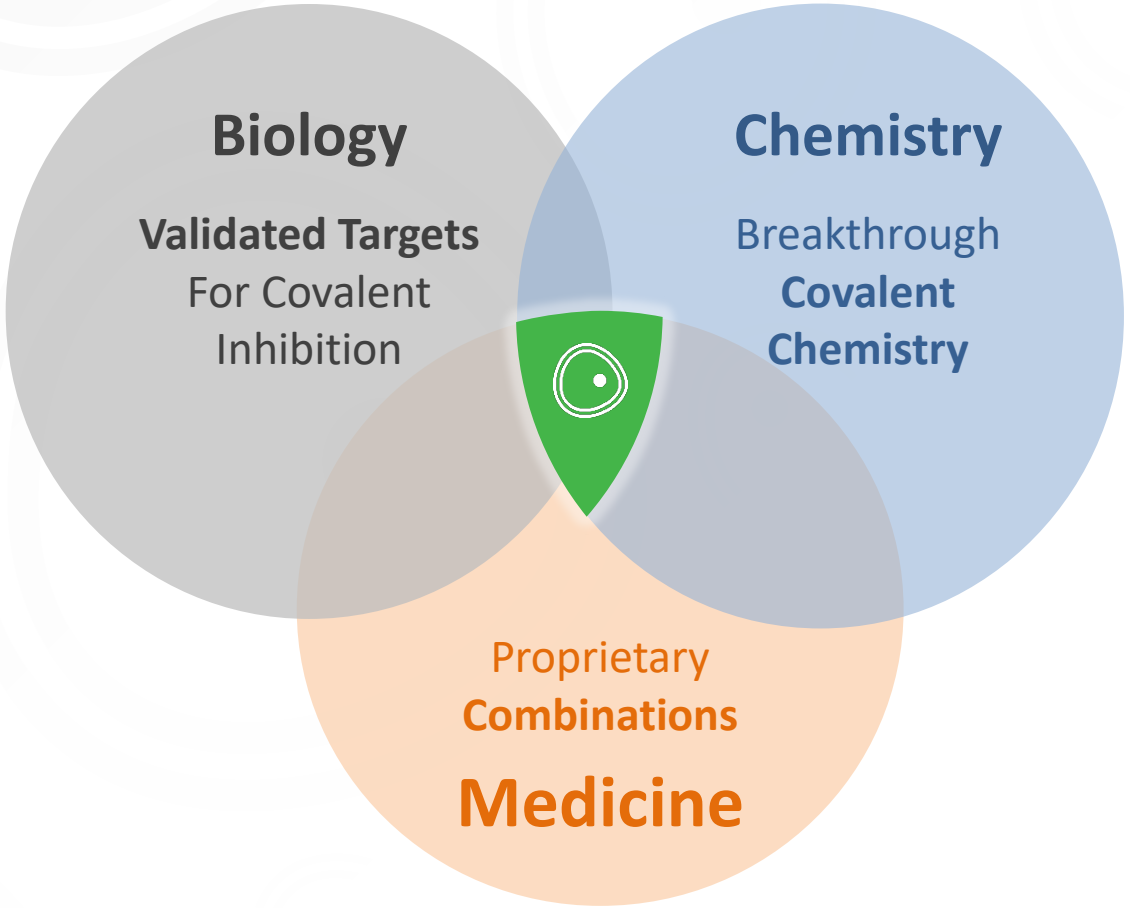
Franco Valle
Chief Financial Officer

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

AMTAGVI™ (lifileucel) Suspension for IV infusion

*Note: icovamenib is an investigational new drug

“We Aim to Cure” by addressing validated targets with breakthrough covalent chemistry in proprietary combinations



Validated Targets

Drugs pursuing **Validated Disease Targets** have a ~2x higher likelihood of approval than molecules pursuing a new mechanism of action

Sources: Nelson et al. (2015) Nat Genet.; Thomas et al. (2016) BIO; In a Landscape of 'Me Too' Drug Development, What Spurs Radical Innovation? HBS Weekly Review (Jun 2018)

Covalent Inhibitors

Covalent Small Molecule Inhibitors provide deep target inactivation and a wider therapeutic window, allowing for longer duration on therapy

Sources: Singh et al. (2011) Nature Reviews Drug Discovery; Cheng et al. (2020) Journal of Hematology & Oncology; Strelow (2017) SLAS Discovery; Kalgutkar & Dalvie (2012) Expert Opin. Drug Discov.;

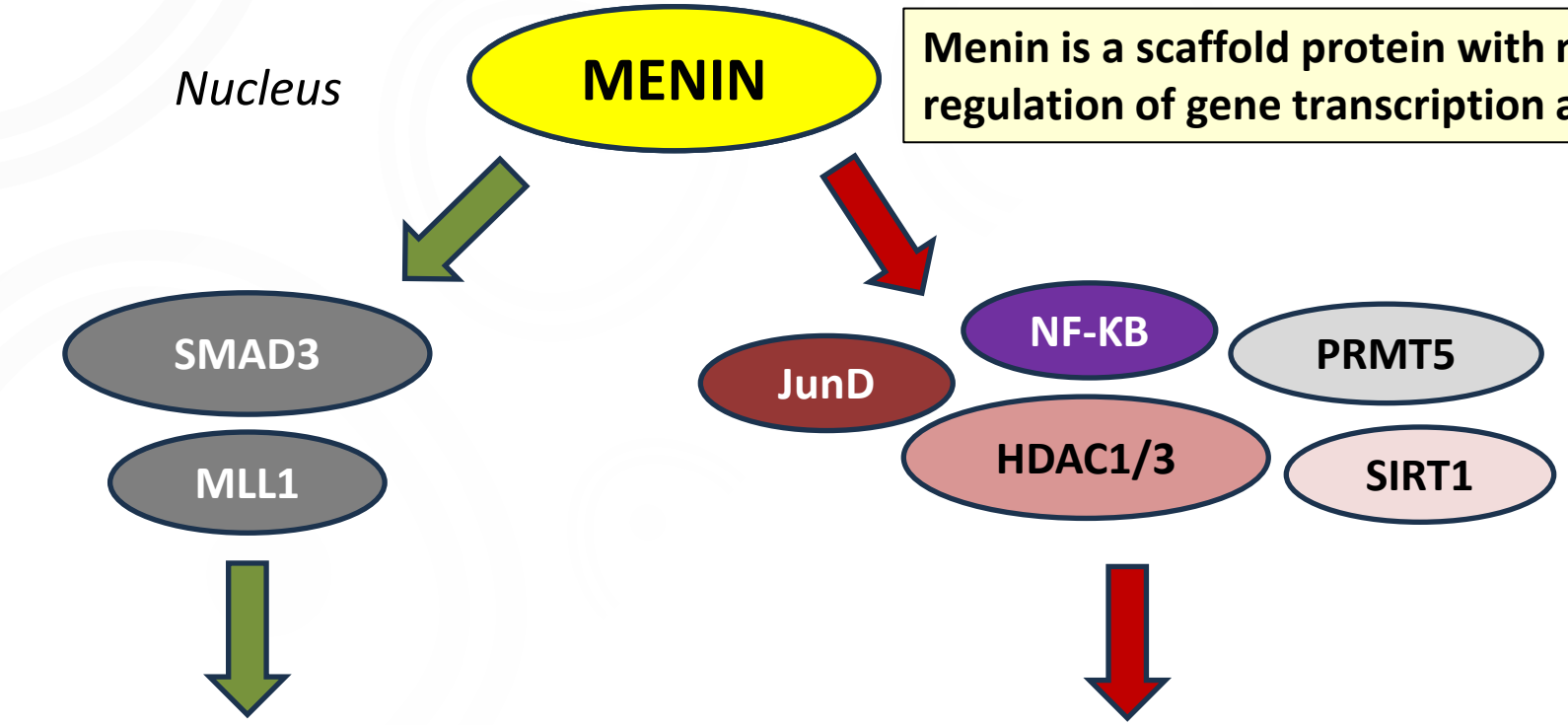
Proprietary Combinations

Combination Therapy with non-overlapping resistance mechanisms results in more durable responses and better outcomes

Sources: Palmer et al. (2019) eLife; Mokhtari et al. (2017) Oncotarget

Menin's role in beta cell proliferation and glucose homeostasis

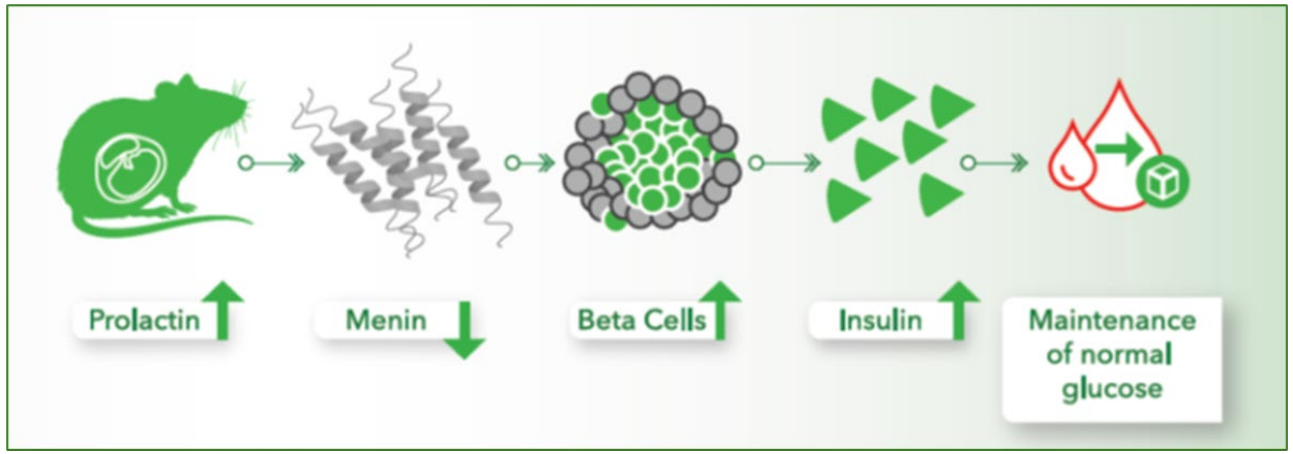
Menin's role in nuclear complexes regulate beta cell proliferation



Suppression of beta cell proliferation

Menin is downregulated by prolactin during pregnancy allowing for beta cell replication and prevention of gestational diabetes

- In 2007, Stanford University researchers found that menin regulated adaptive islet growth in pregnant mice
- Prolactin, a hormonal regulator of pregnancy, repressed beta cell menin levels and stimulated beta cell proliferation



Science
AAAS

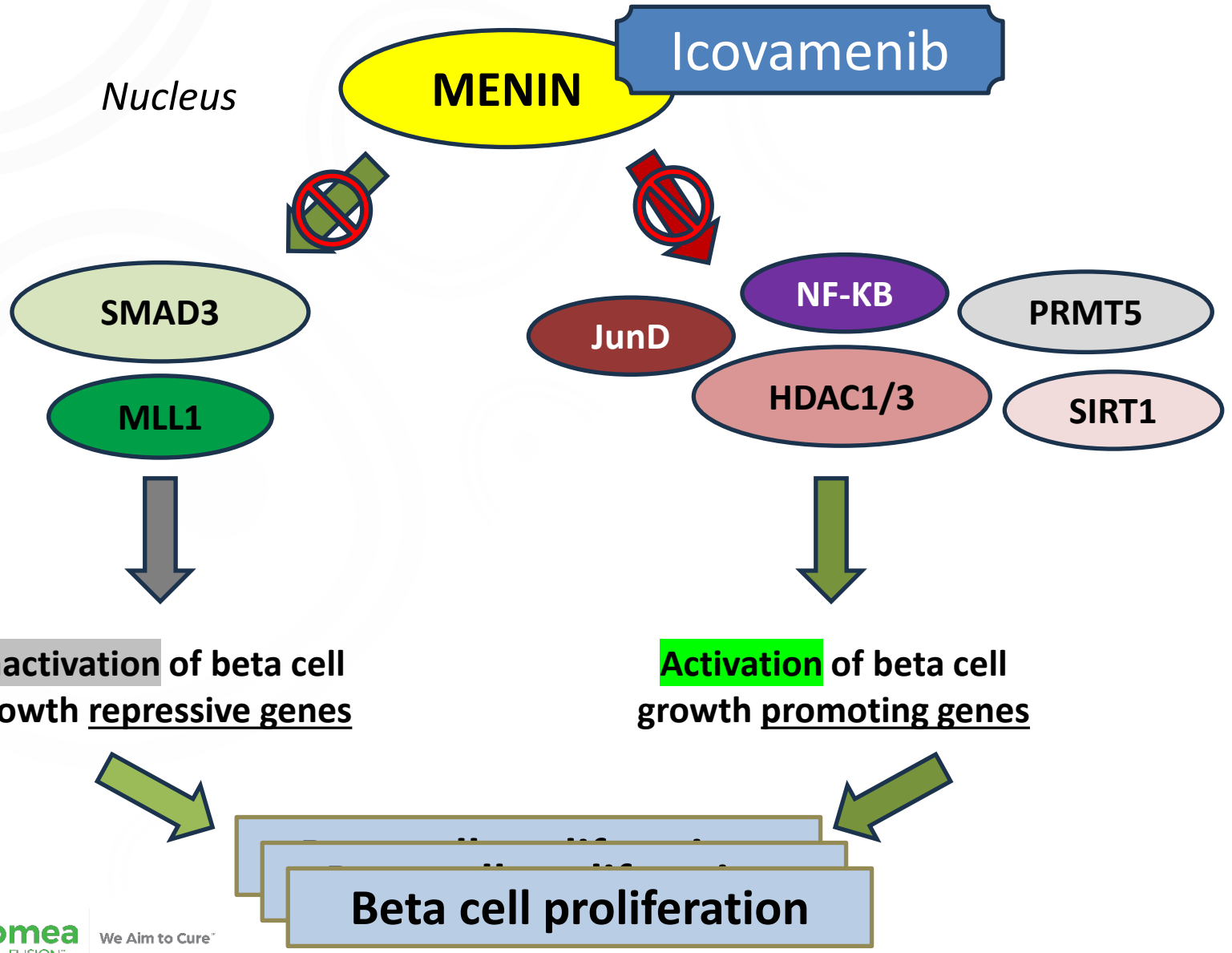
Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

Satyajit K. Karnik,[1] Hainan Chen,[1*] Graeme W. McLean,[1*] Jeremy J. Heit,[1*] Xueying Gu,[1] Andrew Y. Zhang,[1] Magali Fontaine,[2] Michael H. Yen,[1,3] Seung K. Kim[1,3]†

During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands, but the mechanisms regulating adaptive islet growth in this setting are poorly understood. Here we show that menin, a protein previously characterized as an endocrine tumor suppressor and transcriptional regulator, controls islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet β-cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal β-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes. Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated β-cell proliferation. These results expand our understanding of mechanisms underlying diabetes pathogenesis and reveal potential targets for therapy in diabetes.

Karnik SK, et al. Science. 2007;318:806-809

Icovamenib: A potent and selective oral covalent menin inhibitor



Preclinical Evidence:

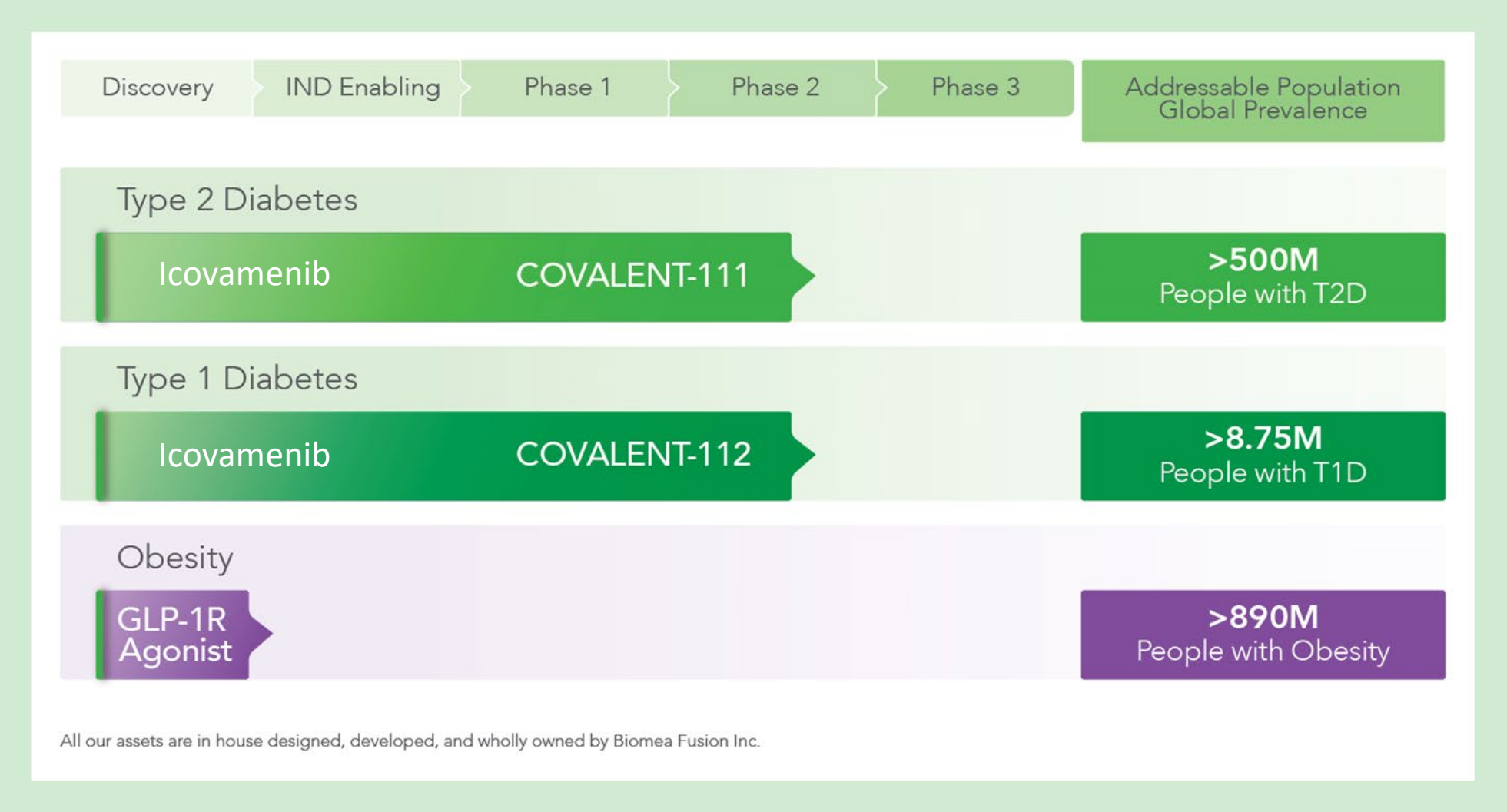
- Short-term icovamenib treatment in diabetic rat models (ZDF and STZ)
- Result: Durable glycemic control observed[1,2]

Clinical Evidence:

- 4-week daily icovamenib treatment
  - Improved glycemic control at Week 26 (22 wks post-treatment)
  - Generally safe and well-tolerated[3]

1. Butler T. et al. Diabetes. 2022; 71 (Supplement_1): 851–P
2. Somanath P. et al. Diabetes. 2022; 71 (Supplement_1): 113–LB
3. Abitbol A, et al. (ATTD 2024, March 6, 2024)

Our product pipeline includes diabetes and obesity

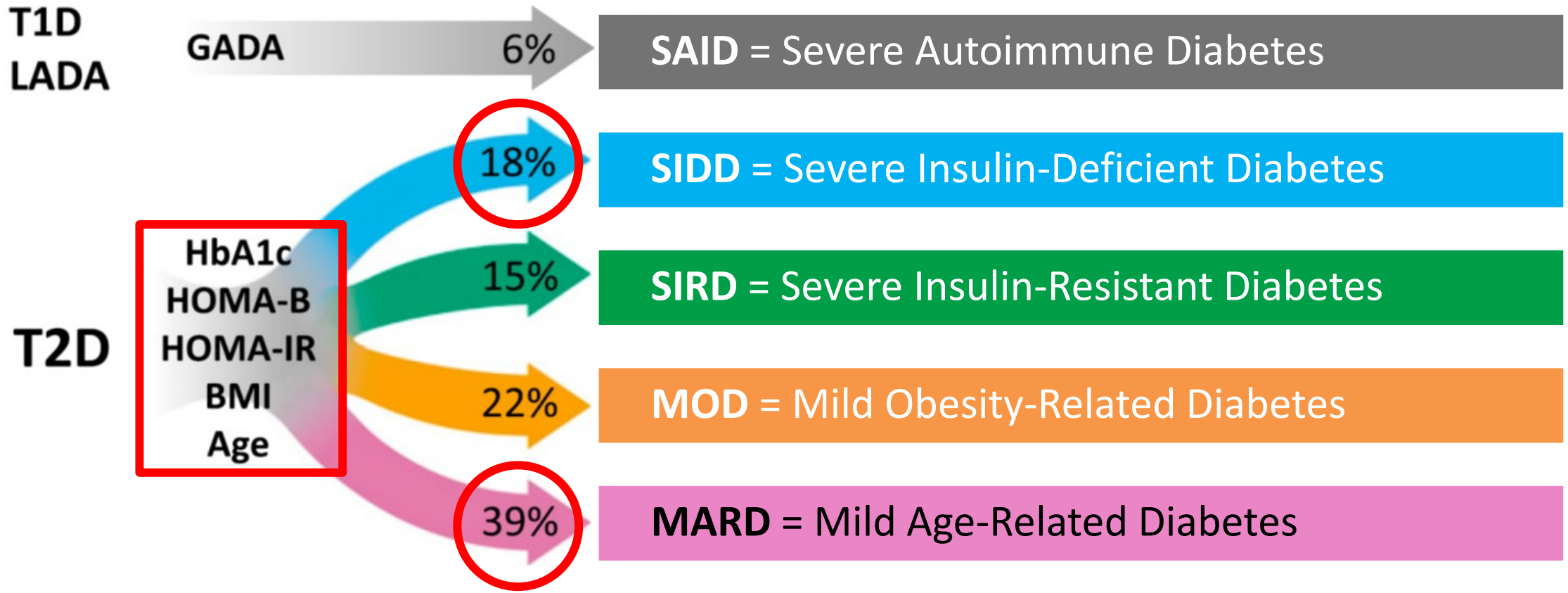


Icovamenib – An investigational agent focusing on beta cell health

Icovamenib: First-in-Class Agent with a Differentiated Profile

- Oral Small Molecule
- Complementary Agent to Available Diabetes Therapies
- Short-Treatment Duration
- Well-Tolerated Profile To Date
- Disease-Modifying Potential Addressing the Root Cause of Diabetes
- Durable Glycemic Control
- Broad Application Across Persons with Diabetes

“While diabetes is diagnosed on the basis of a single metabolite, glucose, hyperglycemia can arise due to multiple complex etiological processes that can vary between individuals.”[1,2]



1. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019;42(Suppl. 1):S13–S28
2. Ahlqvist E, et al. Diabetes 2020;69:2086–2093
3. Ahlqvist E, et al. Lancet Diabetes Endocrinol. 2018;6:361-369
4. Zaghlool SB, et al. Nat Commun. 2022;13:7121

One Size Does Not Fit All: Subtypes of Type 2 Diabetes

Alice YY Cheng, MD, FRCPC

@AliceYYCheng

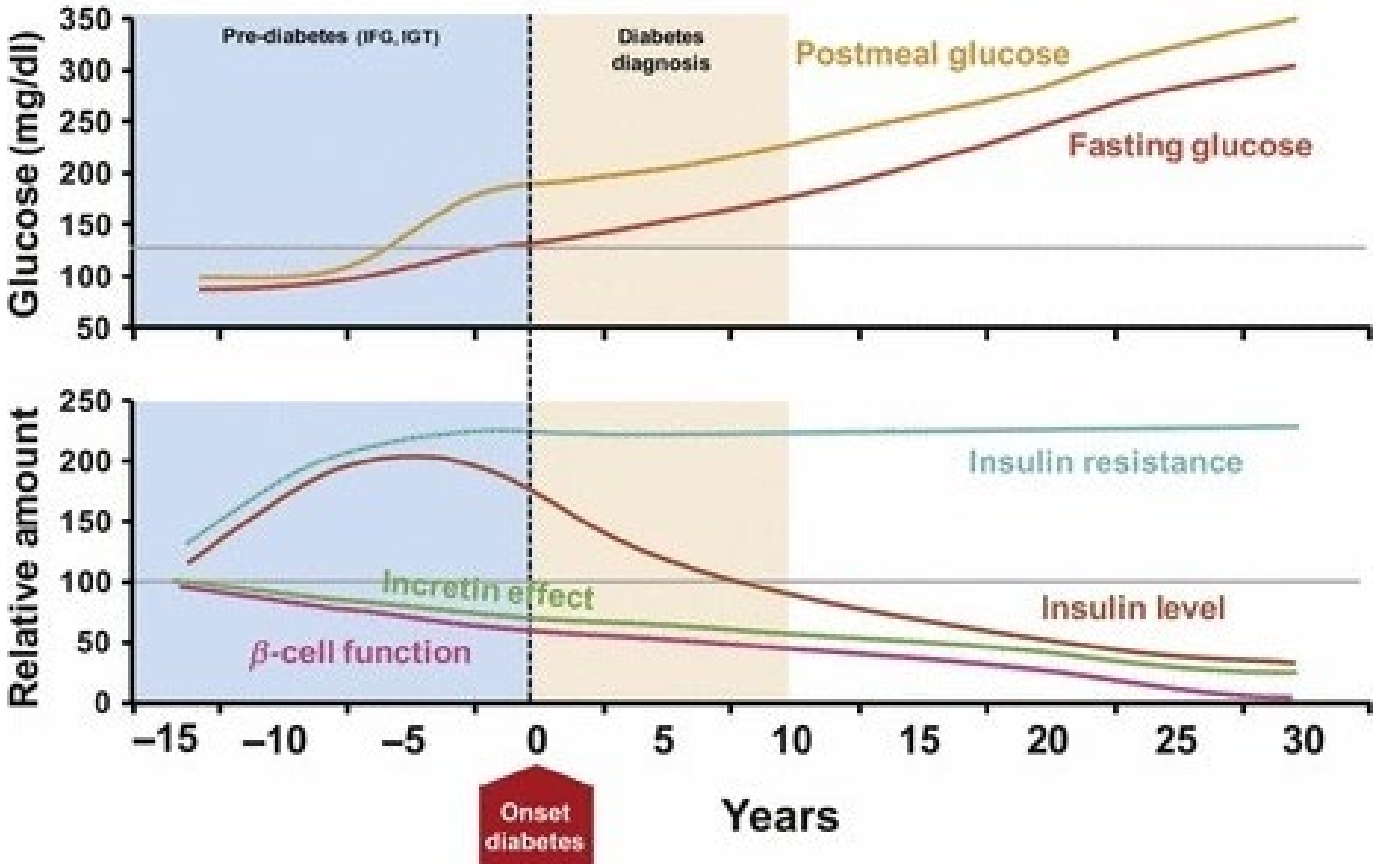
Medicine
UNIVERSITY OF TORONTO

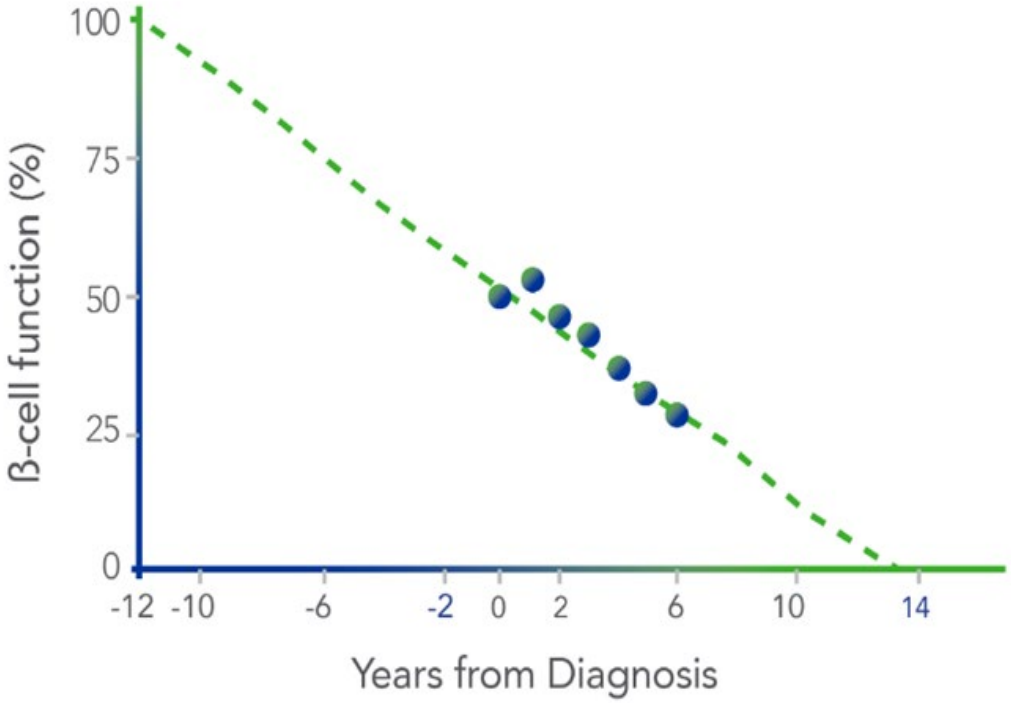
INSULIN 100

Disclosures (Alice Cheng)

- **Advisory panel / consulting**: Abbott, Bayer, Biomea, Boehringer Ingelheim, Dexcom, Eisai, Eli Lilly, Insulet, HLS Therapeutics, Novo Nordisk, Sanofi, Vertex
- **Speaker or CME development**: Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, GSK, HLS Therapeutics, Medtronic, Novo Nordisk, Pfizer, Sanofi
- **Clinical trial:** Sanofi, Novo Nordisk, Applied Therapeutics

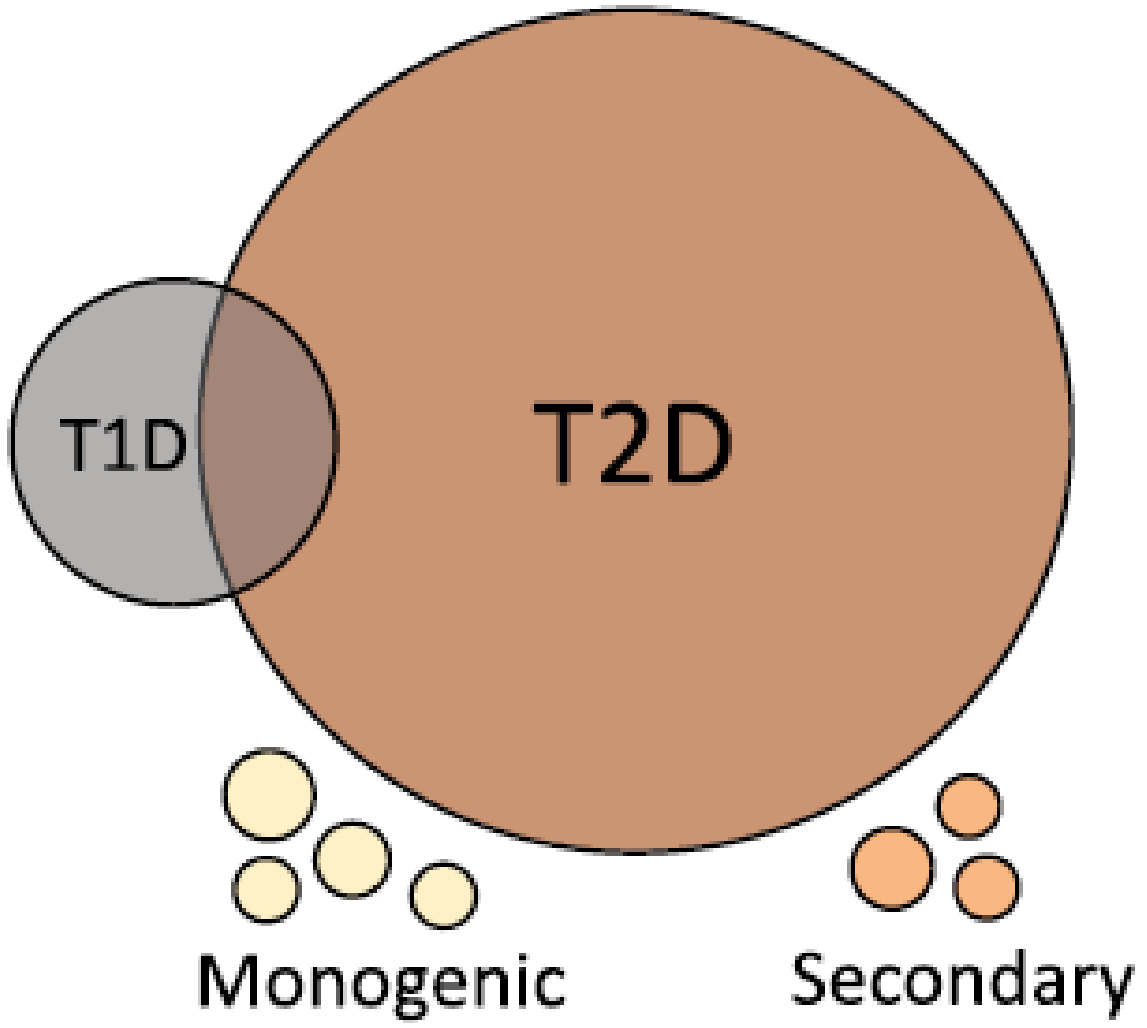
Natural history of type 2 diabetes



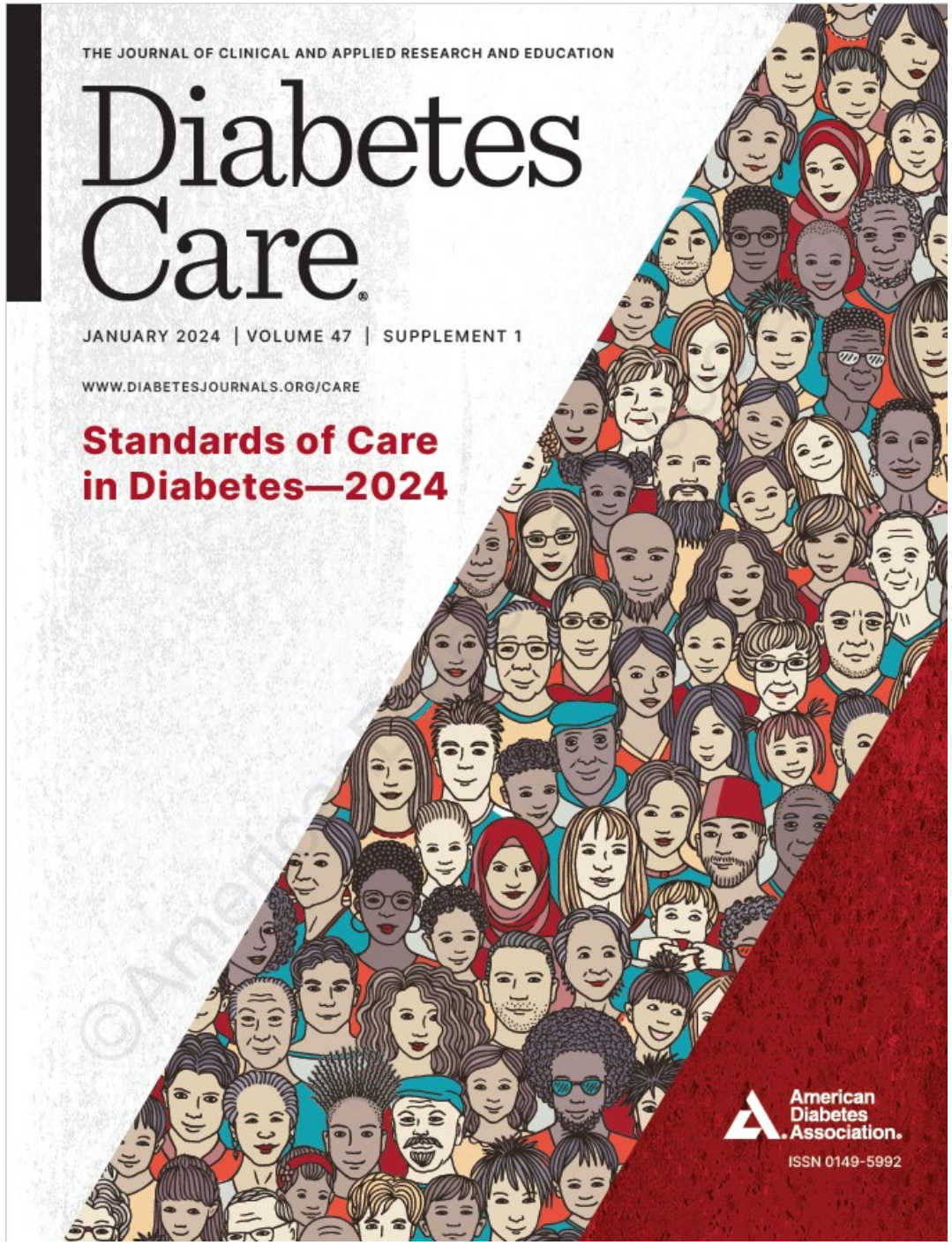


DeFronzo RA. *Diabetes.* 2009;58(4):773-795.

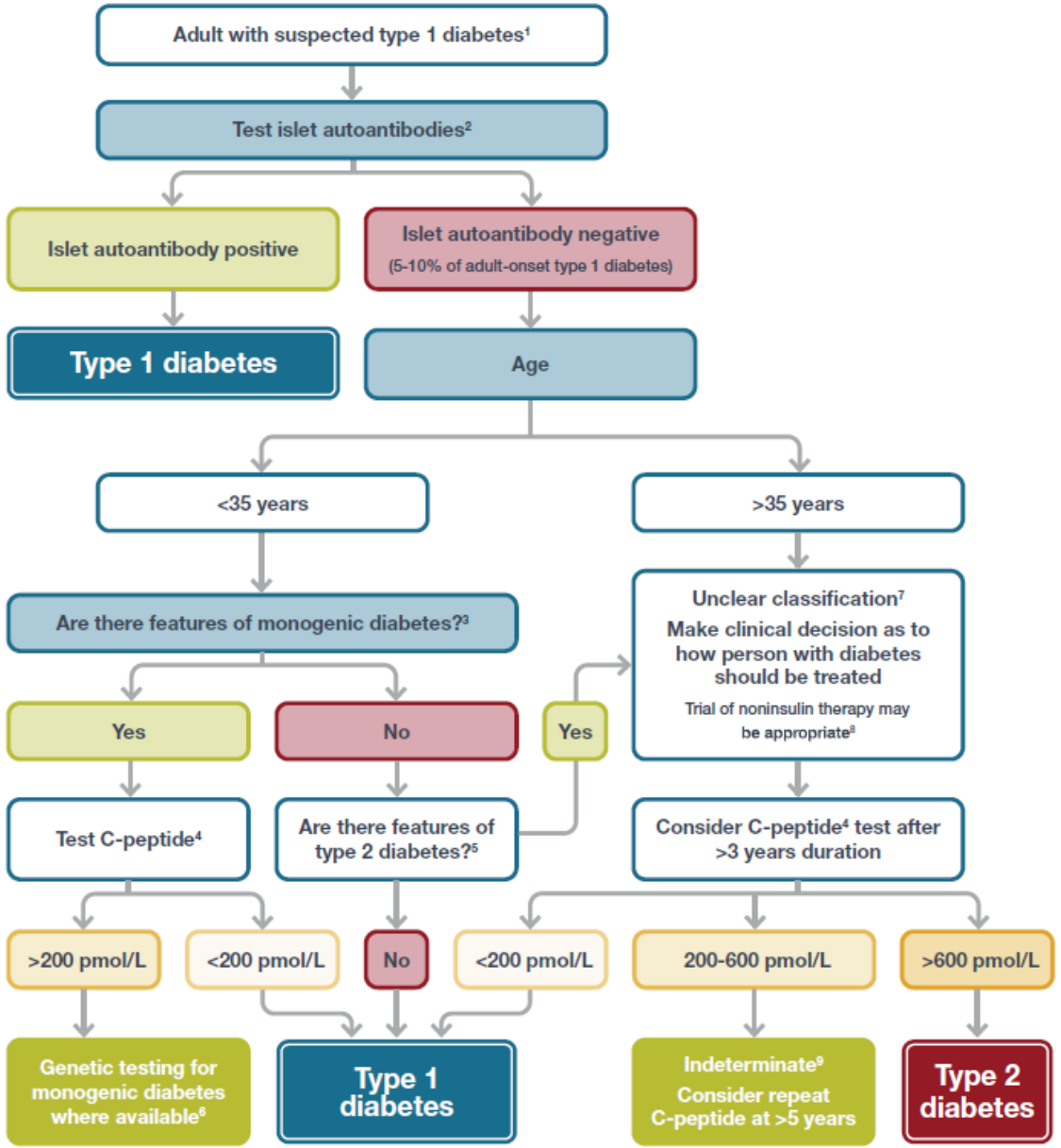
Remember When...?



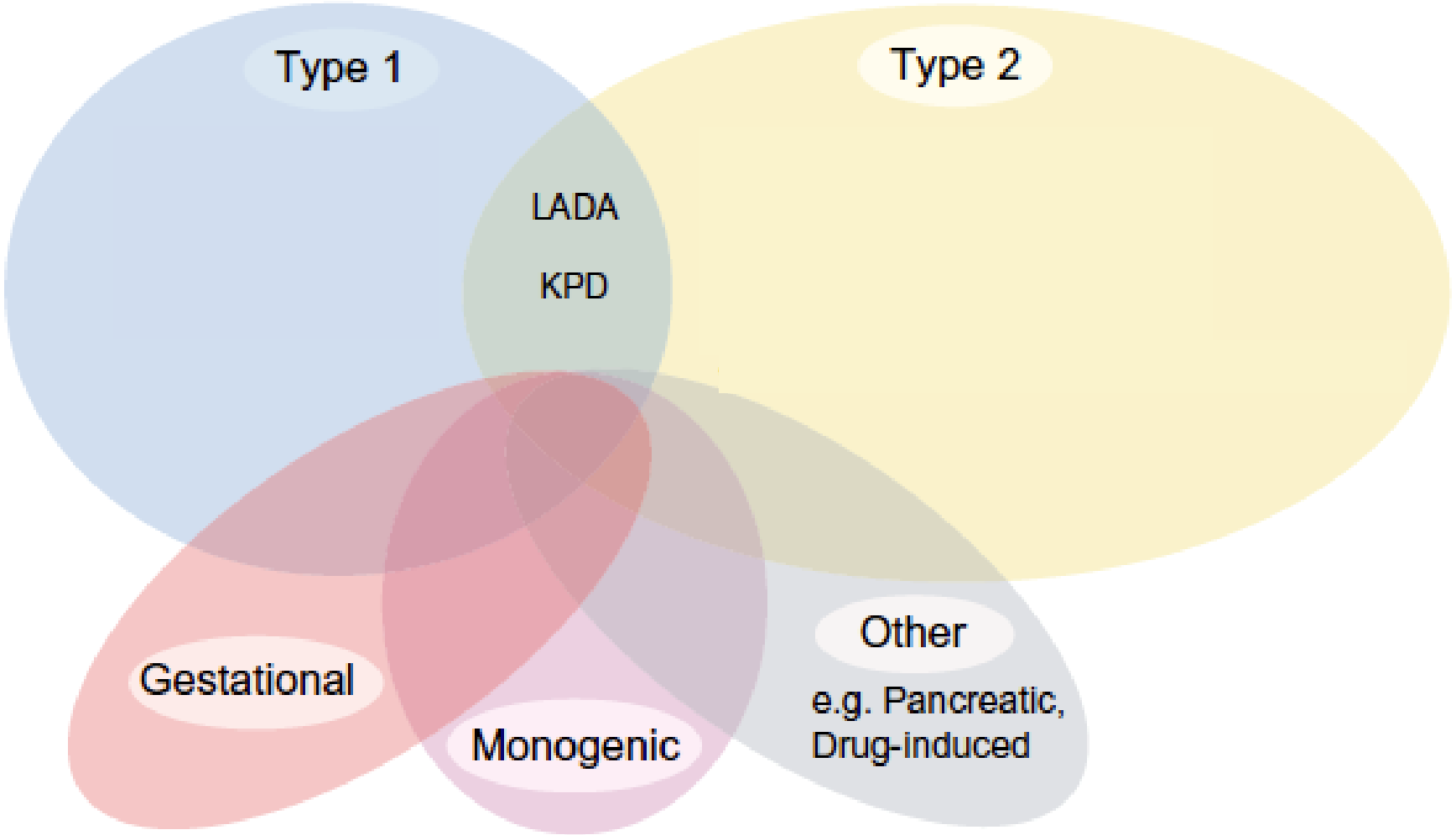
Ahlqvist E et al. Diabetes 2020;69:2086-93.



Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations



Not that simple … lots of overlap



LADA: latent autoimmune diabetes of adult; KPD: ketosis prone diabetes

Deutsch AJ et al Diabetologia 2022;65:1758-69.

Heterogeneity in Type 2 diabetes

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*

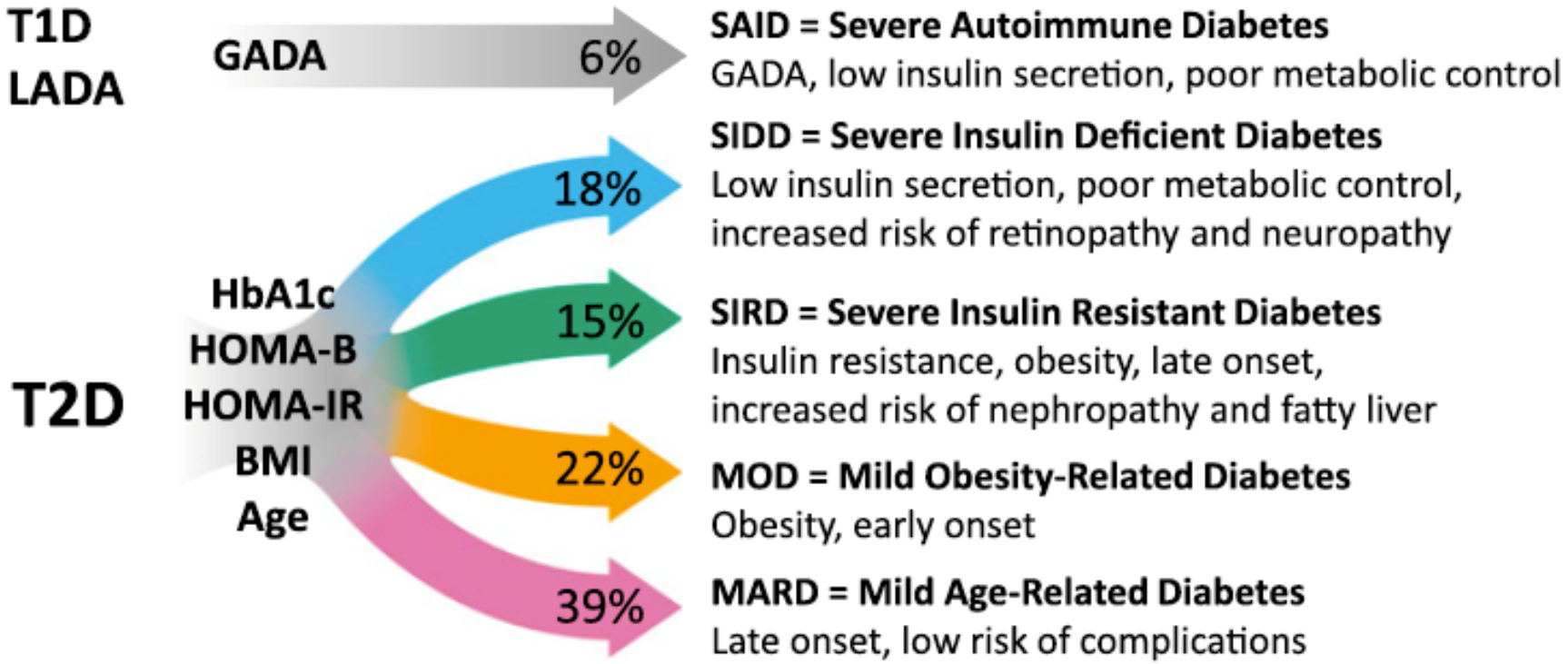
- Anti-GAD antibodies
- Age at diagnosis
- BMI
- A1c
- Beta-cell function (HOMA2-B)*
- Insulin resistance (HOMA2-IR)*

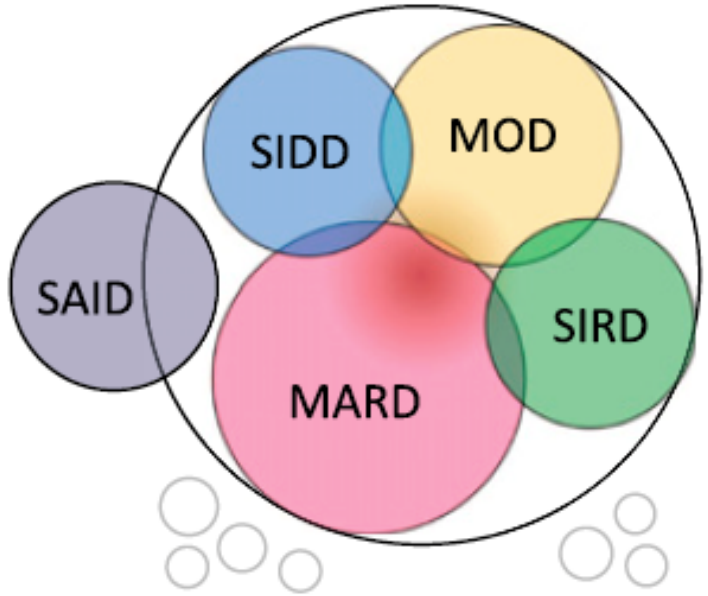
* Require measurement of fasting glucose, C-peptide, fasting insulin

1. Severe autoimmune diabetes
2. Severe insulin-deficient diabetes
3. Severe insulin-resistant diabetes
4. Mild obesity-related diabetes
5. Mild age-related diabetes

Ahlqvist E et al. Lancet Diab Endocrinol 2018:6:361-69.

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





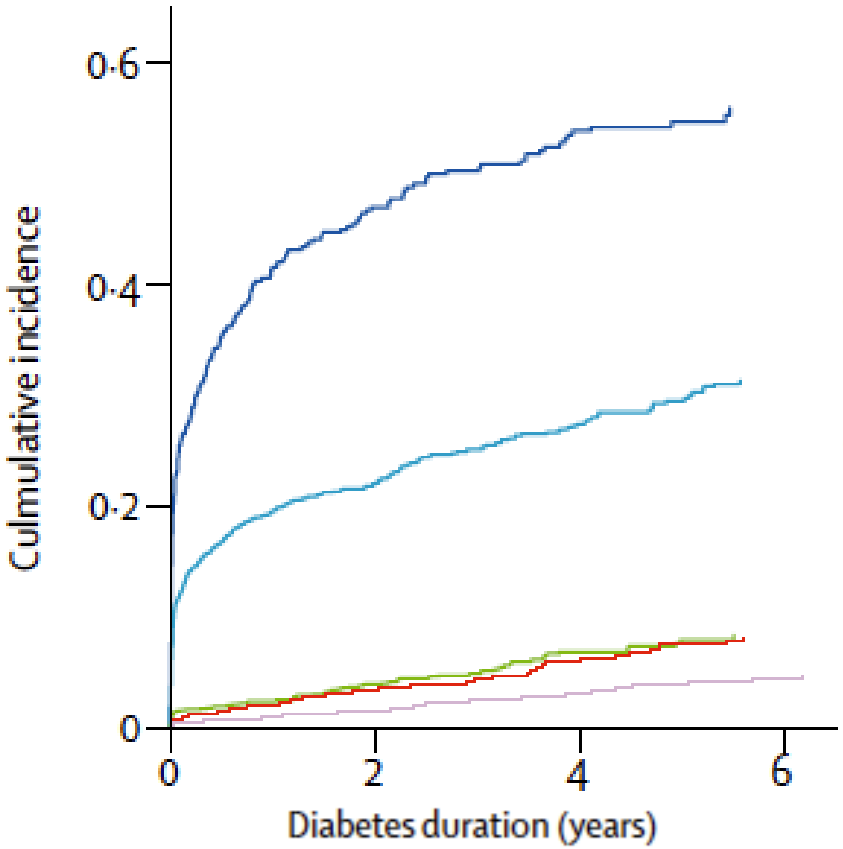
Based on Swedish ANDIS cohort

ANDIS: All New Diabetics in Scania

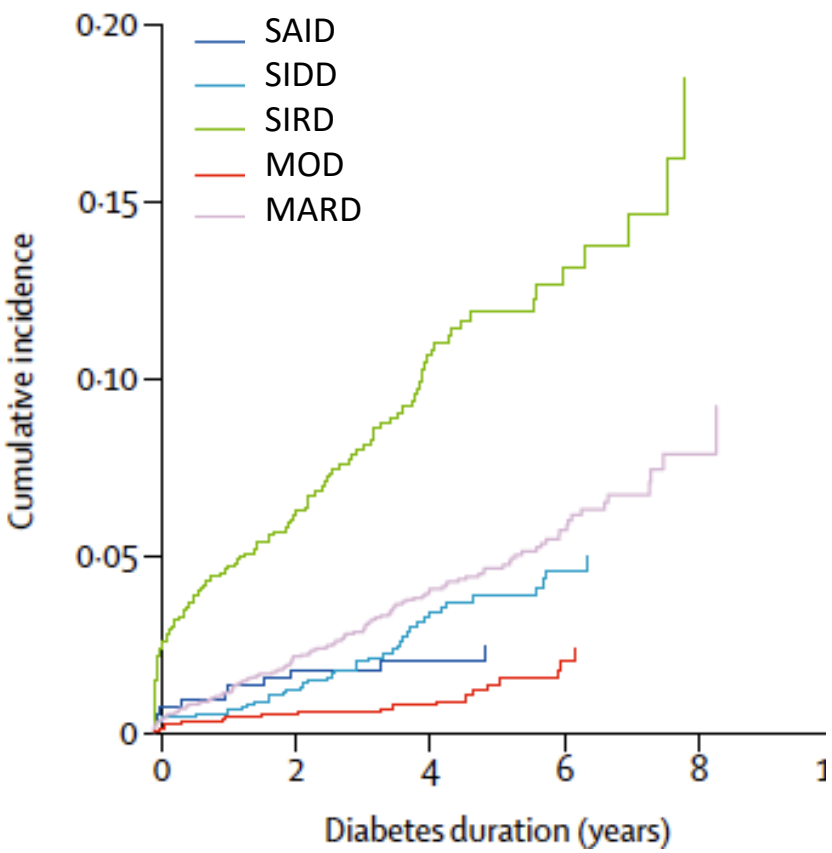
Ahlqvist E et al. Lancet Diab Endocrinol 2018:6:361-69.
Ahlqvist E et al. Diabetes 2020;69:2086-93

Diabetes subtype impact treatment and prognosis

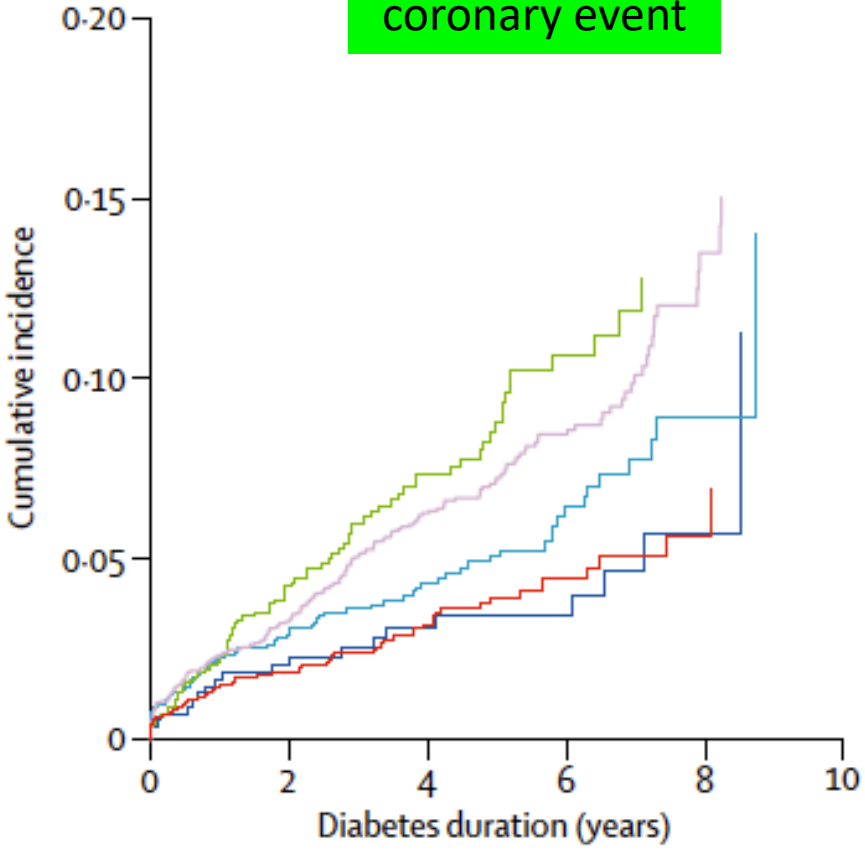
Time to insulin



Time to CKD



Time to coronary event



SAID Severe autoimmune diabetes; SIDD Severe insulin deficient diabetes; SIRD Severe insulin resistance diabetes; MOD mild obesity related diabetes; MARD mild age related diabetes

Ahlqvist E et al. Lancet Diab Endocrinol 2018:6:361-69.

DDZ
German Diabetes Center

DDZ Diabetes-Cluster-Tool

Deutsch

GAD-Antibodies

Not Present

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

Age at diagnosis (years)

42

BMI (kg/m²)

25

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

mg/dl

Fasting plasma glucose (fasting blood sugar)

180

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

ng/ml

Fasting C-Peptide

5

HbA1c (%)

8.5

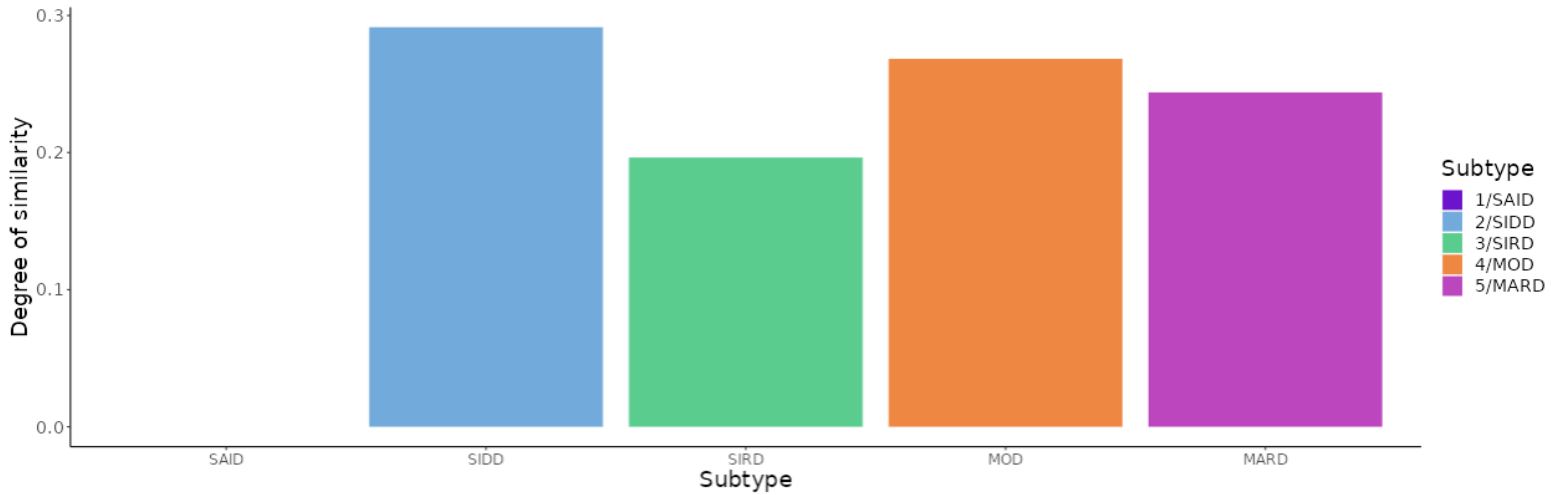
Sex

Male

Tool | Background information

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

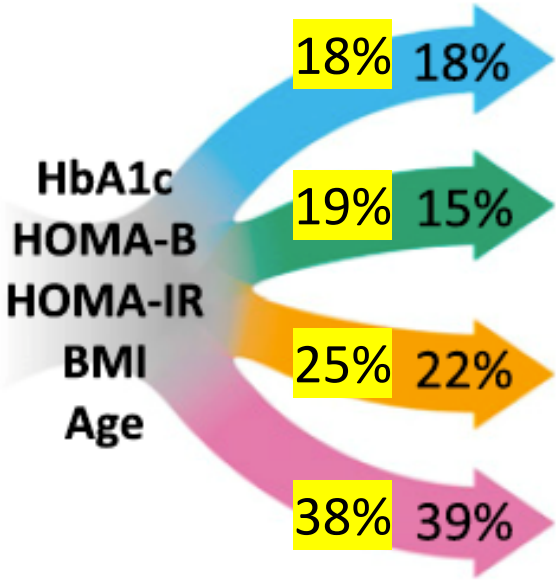
References

Ahlqvist, E., Storm, P., Käräjämäki, A., Martinell, M., Dorkhan, M., Carlsson, A., ... & Groop, L. (2018). Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *The Lancet Diabetes & Endocrinology* 6(5), 361-369.

Zaharia, O. P., Strassburger, K., Strom, A., Bönhof, G. J., Karusheva, Y., Antoniou, S., ... & Roden, M. (2019). Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *The Lancet Diabetes & Endocrinology* 7(9), 684-694.

Identifying subtypes of type 2 diabetes mellitus based on real-world electronic medical record data in China

EMR data from tertiary hospital in Beijing, China (2000-2022). n= 2652 people with T2D

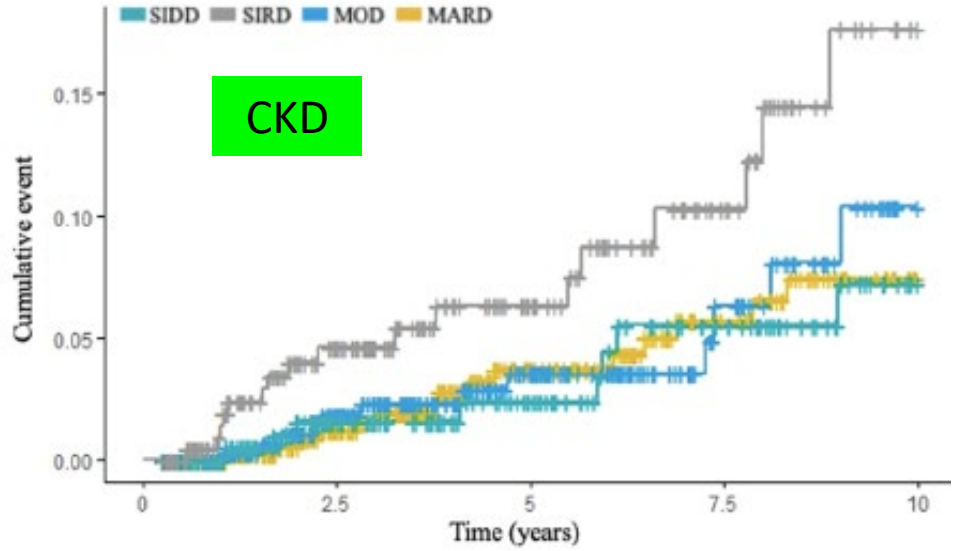


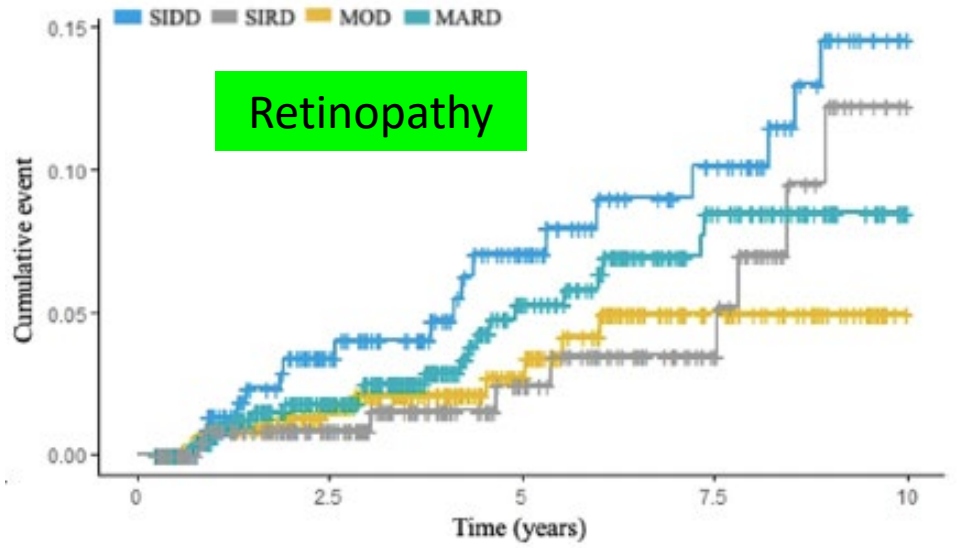
SIDD = Severe Insulin Deficient Diabetes
Low insulin secretion, poor metabolic control, increased risk of retinopathy and neuropathy

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

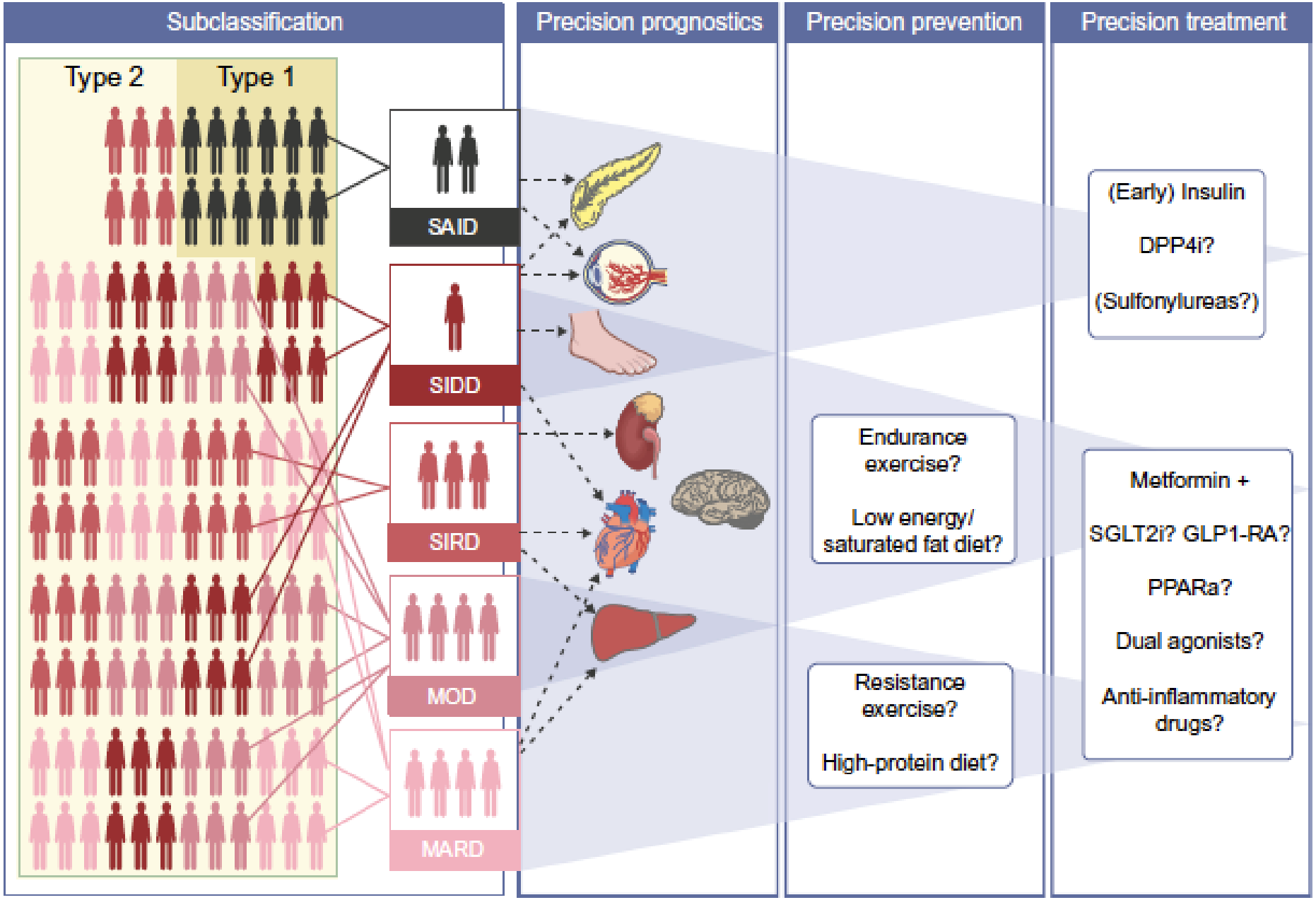
MOD = Mild Obesity-Related Diabetes
Obesity, early onset

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





Wang JY et al. Diab Res Clin Pract 2024 Nov;217:111872.



Herder C, Roden M. Diabetologia 2022;65:1770-81.

Diabetes Management Based on the Phenotype and Stage of the Disease: An Expert Proposal from the AGORA Diabetes Collaborative Group

	STAGE 1 Genetics-preclinical biomarkers	STAGE 2 IGT/IFG/HbA1c 5.7–6.5 % DL/HBP	STAGE 3 HbA1c > 6.5 % DL/HTA No clin. comp. Low insulin secretion	STAGE 4 HbA1c > 8% DL/HTA Clin. Comp.
Severe insulin-deficient diabetes (SIDD) 	• Lower age • No insulinresistance • Normal insulin secretion *(C-peptide values > 0.7 nmol/L)* • Normal adiposity	• Middle age • No insulinresistance • Slightly Low insulin secretion *(C-peptide values 0.3–0.7 nmol/L)* • Normal adiposity	• Middle age • No insulinresistance • Very low insulin secretion *(C-peptide values < 0.3 nmol/L)* • Normal adiposity	• Since middle age • No insulinresistance • Very low insulin secretion *(C-peptide values < 0.3 nmol/L)* • Normal/overweight • **Increased risk of retinopathy and nephropathy**
Follow-up	Annually	2–3/Year CGM		
Recommended management	NA	Prandial/basal insulin	Basal-bolus insulin/ISCI	
Treatment goals	**HbA1c < 5.7%*** **LDL-c < 70 BP < 130/70** **Normal weight**	**HbA1c 5.7*–6.5 %LDL-c** **< 70 BP < 130/70** **Normal weight/-10%**	**HbA1c < 6.5%** **LDL-c < 70 BP < 130/70** **Normal weight/-10%**	**HbA1c < 8%** **LDL-c, BP, weight:** **Individualize**
Severe insulin resistance (SIRD) 	• Middle age • Insulin resistance • Hyperinsulinism • Visceral adiposity	• Middle age • Insulin resistance • Hyperinsulinism • Visceral adiposity	• Middle/late age • Insulin resistance • Hyperinsulinism/partial insulin deficiency • Visceral adiposity	• Middle/late age • Insulin resistance • Low insulin secretion • Visceral adiposity • **Increased risk of kidney disease, fatty liver and CVD**
Follow-up	2–3/Year			
Recommended management	Intensive LSM /Bx Surgery/ DMD + metf/pio			Intensive LSM DMDs + metf/pio + basal insulin
Treatment goals	**HbA1c < 5.7%*** **LDL-c < 70 BP < 130/70** **Normal weight/-10%**	**HbA1c 5.7*–6.5%LDL-c** **< 70 BP < 130/70** **Normal weight/-10%**	**HbA1c < 6.5%** **LDL-c < 70 BP < 130/70** **Normal weight/-10%**	**HbA1c < 8%** **LDL-c, BP, weight:** **Individualize**

*Or Upper limit of normality for HbA1c

Gomez-Peralta F et al. J Clin Med 2024 Aug 16;13:4839.

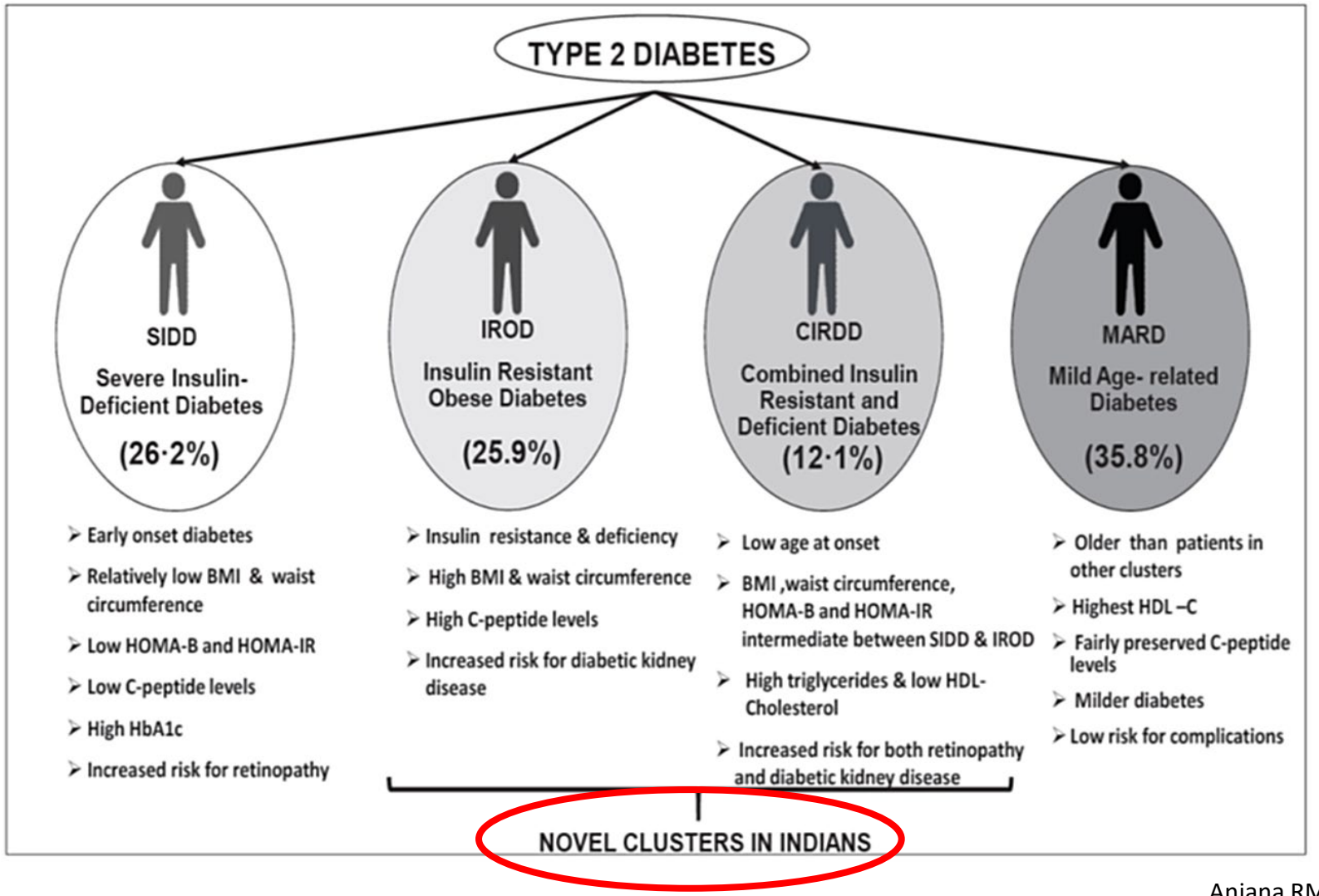
Diabetes Management Based on the Phenotype and Stage of the Disease: An Expert Proposal from the AGORA Diabetes Collaborative Group

	STAGE 1 Genetics-preclinical biomarkers	STAGE 2 IGT/IFG/HbA1c 5.7–6.5 DL/HBP	STAGE 3 HbA1c > 6.5 DL/HTA No clin. comp. Low insulin secretion	STAGE 4 HbA1c > 8% DL/HTA Clin. Comp.
Mild obesity-related diabetes (MOD) 	• Low age • No insulin resistance • Normal insulin secretion • Subcutaneous adiposity	• Middle age • No Insulin resistance • Hyperinsulinism • Subcutaneous adiposity	• Middle age • Insulin resistance • Partial insulin deficiency • Subcutaneus + Visceral adiposity	• Late age • Insulin resistance • Low insulin secretion • Subcutaneus + Visceral adiposity • **Mechanical complications**
Follow-up	Annually		2–3/Year	
Recommended management	LSM /Bx Surgery DMDs		LSM DMDs + metf/pio	LSM DMDs + metf/pio + basal insulin
Treatment goals	**HbA1c < 5.7%*** **LDL-c < 70 BP < 130/70** **Normal weight/-10%**	**HbA1c 5.7*–6.5%LDL-c < 70 BP < 130/70** **Normal weight/-10%**	**HbA1c < 6.5%** **LDL-c < 70 BP < 130/70** **Normal weight/-10%**	**HbA1c < 8%** **LDL-c, BP, weight: Individualize**
Mild age-related diabetes (MARD) 	• Late onset/elderly • No insulinresistance • Normal insulin secretion • Normal adiposity	• Late onset/elderly • No insulinresistance • Slightly Low insulin secretion *(C-peptide values 0.3–0.7 nmol/L)* • Normal adiposity	• Late onset/elderly • No insulinresistance • Low insulin secretion • Normal adiposity/sarcopenia	• Late onset/elderly • No insulinresistance • Low insulin secretion • Underweight risk /sarcopenia • **Low risk of complications**
Follow-up	Annually		2/Year	
Recommended management	NA		Nutritional support Safer antidiabetic drugs	Nutritional support Safer antidiabetic drugs + basal insulin
Treatment goals	**HbA1c < 7%** **LDL-c, BP, weight: Individualize**	**HbA1c < 7%** **LDL-c, BP, weight: Individualize**	**HbA1c < 7.5%LDL-c, BP, weight: Individualize**	**HbA1c < 8%** **LDL-c, BP, weight: Individualize**

*Or Upper limit of normality for HbA1c

Gomez-Peralta F et al. J Clin Med 2024 Aug 16;13:4839.

New and Unique Clusters of Type 2 Diabetes Identified in Indians



- 50 Centers, N=19,084 T2D
- Age at diagnosis, body mass index, waist circumference, HbA1c, serum TG, serum HDL-C, fasting and stimulated C-peptide

- Unlike Scandinavia, there was no mild obesity-related diabetes (MARD”
- Reduced levels of insulin prominent feature even in the insulin resistant group

Anjana RM, et al. BMJ Open Diab Res Care 2020;8:e001506.
Anjana RM, et al. Journal of the Association of Physicians of India. 2021;68:58-61

RSSDI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2022

typic variables. Attempts[20] to identify similar subtypes of T2DM in the Indian population have led to the identification of four "clusters," two of which are identical to those identified in the Caucasian population and two of which are unique to India. These clusters are:

- Severe insulin-deficient diabetes (SIDD) (characterized by low BMI and waist circumference, poor C-peptide, and high HbA1c)
- Insulin-resistant obese diabetes (IROD) (Novel cluster) (High BMI and waist circumference, preserved C-peptide, and moderately elevated HbA1c)
- Combined insulin resistant and deficient diabetes (CIRDD) (Novel cluster) (Low or normal BMI and waist circumference, preserved C-peptide, high HbA1c and triglycerides)
- Mild age-related diabetes (MARD) (Older age at onset, good C-peptide, good HDL, lower HbA1c)

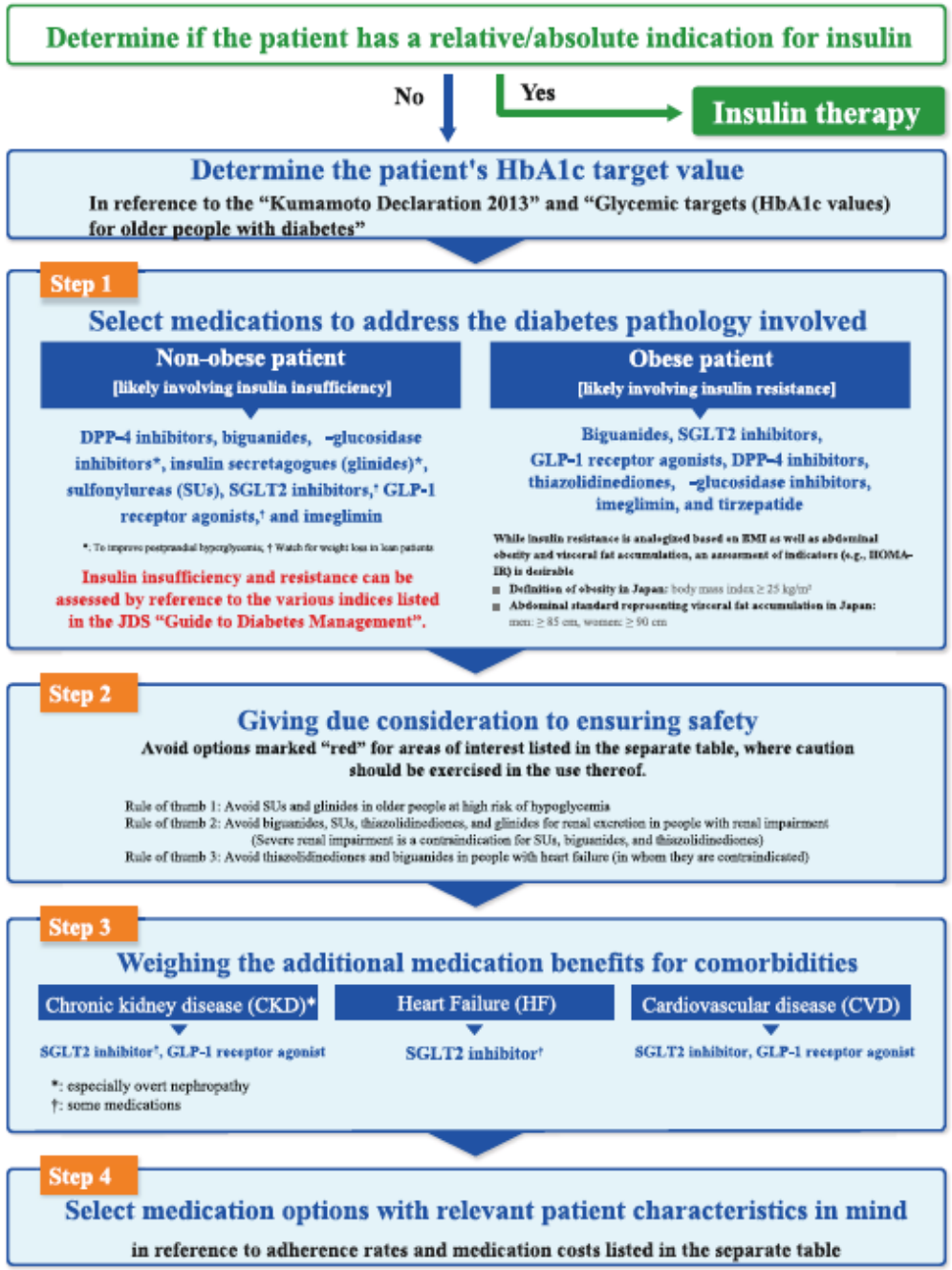
There is some evidence[21] to suggest that these "clusters" differ in the natural history of the disease, risk of complications, and response to treatment.

Makkar BM, et al. Int J Diab Develop Countries 22;42(Suppl 1): S1-S143.

A consensus statement from the Japan Diabetes Society: A proposed algorithm for pharmacotherapy in people with type 2 diabetes – 2nd edition (English version)

Ryotaro Bouchi[1*†], Tatsuya Kondo[2†], Yasuharu Ohta[3†], Atsushi Goto[4], Daisuke Tanaka[5], Hiroaki Satoh[6], Daisuke Yabe[7], Rimei Nishimura[8], Norio Harada[5†], Hideki Kamiya[9†], Ryo Suzuki[10†], Toshimasa Yamauchi[11‡], JDS Committee on Consensus Statement Development

[1]Diabetes and Metabolism Information Center, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan, [2]Department of Diabetes, Metabolism and Endocrinology, Kumamoto University Hospital, Kumamoto, Japan, [3]Division of Endocrinology, Metabolism, Hematological Sciences and Therapeutics, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, [4]Department of Health Data Science, Graduate School of Data Science, Yokohama City University, Yokohama, Japan, [5]Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [6]Department of Diabetes and Endocrinology, Juntendo University Urayasu Hospital, Chiba, Japan, [7]Department of Diabetes, Endocrinology and Metabolism and Department of Rheumatology and Clinical Immunology, Gifu University Graduate School of Medicine, Gifu, Japan, [8]Division of Diabetes, Metabolism and Endocrinology, Jikei University School of Medicine, Tokyo, Japan, [9]Division of Diabetes, Department of Internal Medicine, Aichi Medical University, Nagakute, Japan, [10]Department of Diabetes, Metabolism and Endocrinology, Tokyo Medical University, Tokyo, Japan, and [11]Department of Diabetes and Metabolic Diseases, University of Tokyo Graduate School of Medicine, Tokyo, Japan



Step 1

Select medications to address the diabetes pathology involved

Non-obese patient
[likely involving insulin insufficiency]

DPP-4 inhibitors, biguanides, -glucosidase inhibitors*, insulin secretagogues (glinides)*, sulfonylureas (SUs), SGLT2 inhibitors,† GLP-1 receptor agonists,† and imeglimin

*: To improve postprandial hyperglycemia; † Watch for weight loss in lean patients

Insulin insufficiency and resistance can be assessed by reference to the various indices listed in the JDS "Guide to Diabetes Management".

Obese patient
[likely involving insulin resistance]

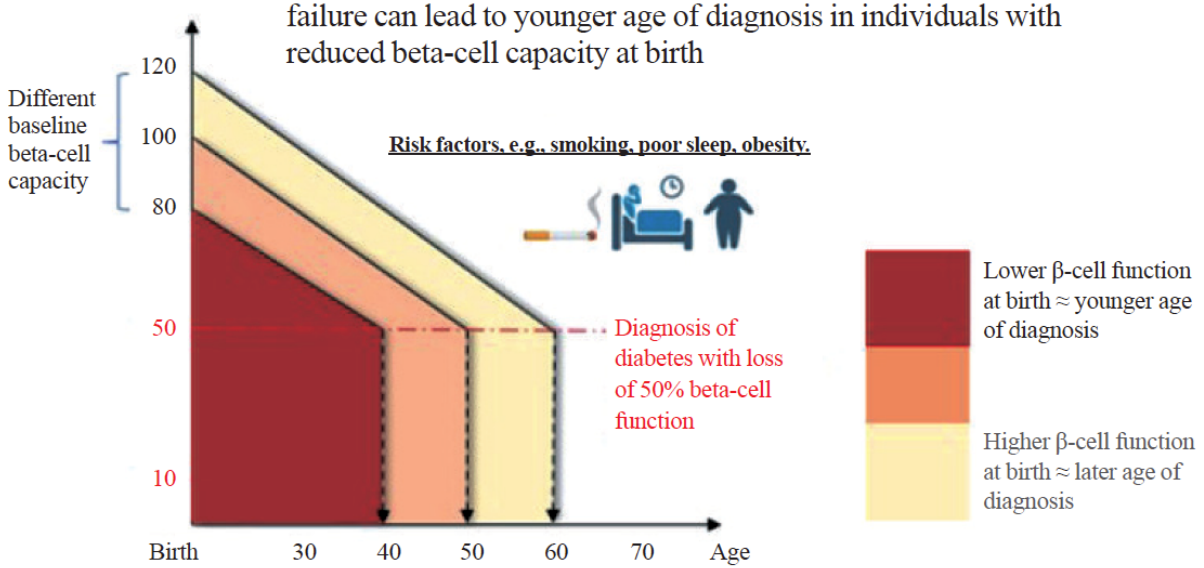
Biguanides, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, thiazolidinediones, -glucosidase inhibitors, imeglimin, and tirzepatide

While insulin resistance is analogized based on BMI as well as abdominal obesity and visceral fat accumulation, an assessment of indicators (e.g., HOMA-IR) is desirable

- **Definition of obesity in Japan:** body mass index ≥ 25 kg/m²
- **Abdominal standard representing visceral fat accumulation in Japan:** men: ≥ 85 cm, women: ≥ 90 cm

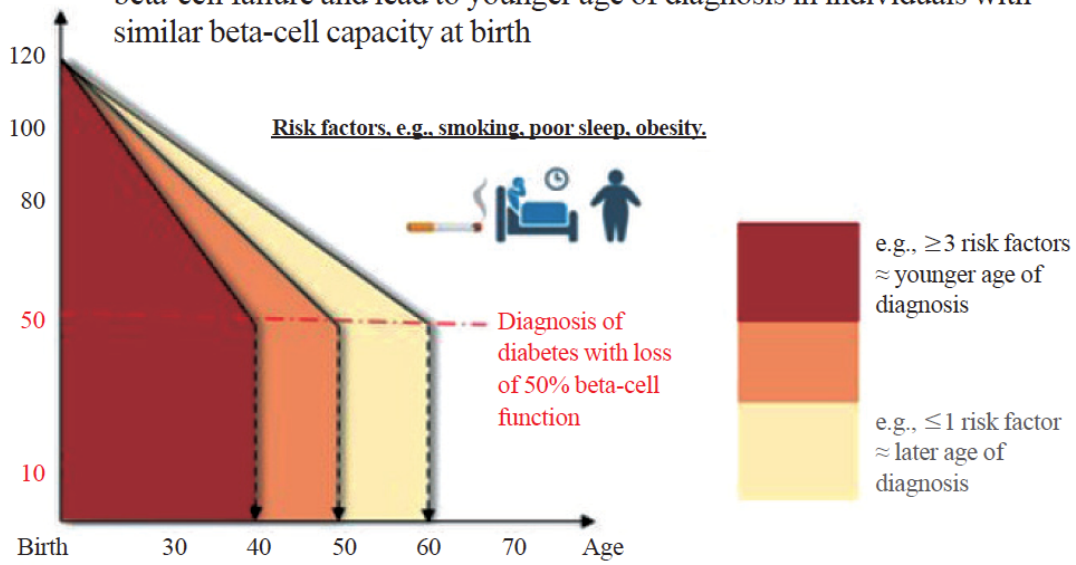
A. Different beta-cell capacity at birth

Same acquired risk factor causing similar trajectory of beta-cell failure can lead to younger age of diagnosis in individuals with reduced beta-cell capacity at birth

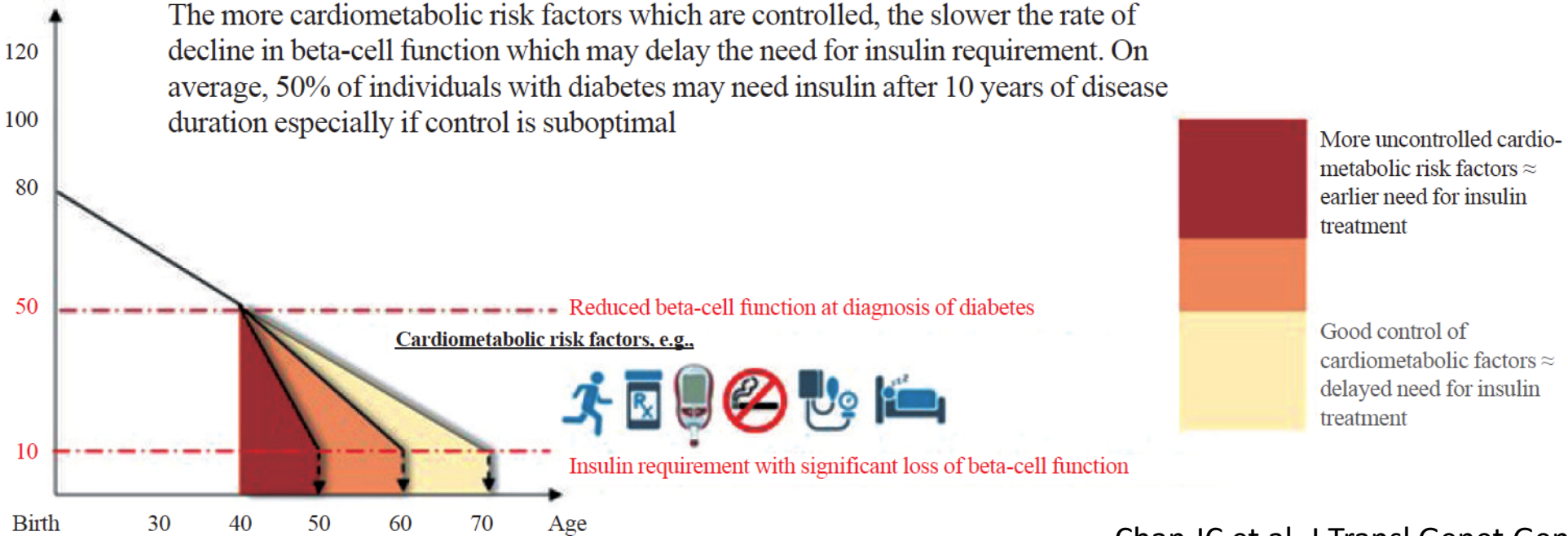


B. Similar beta-cell capacity at birth

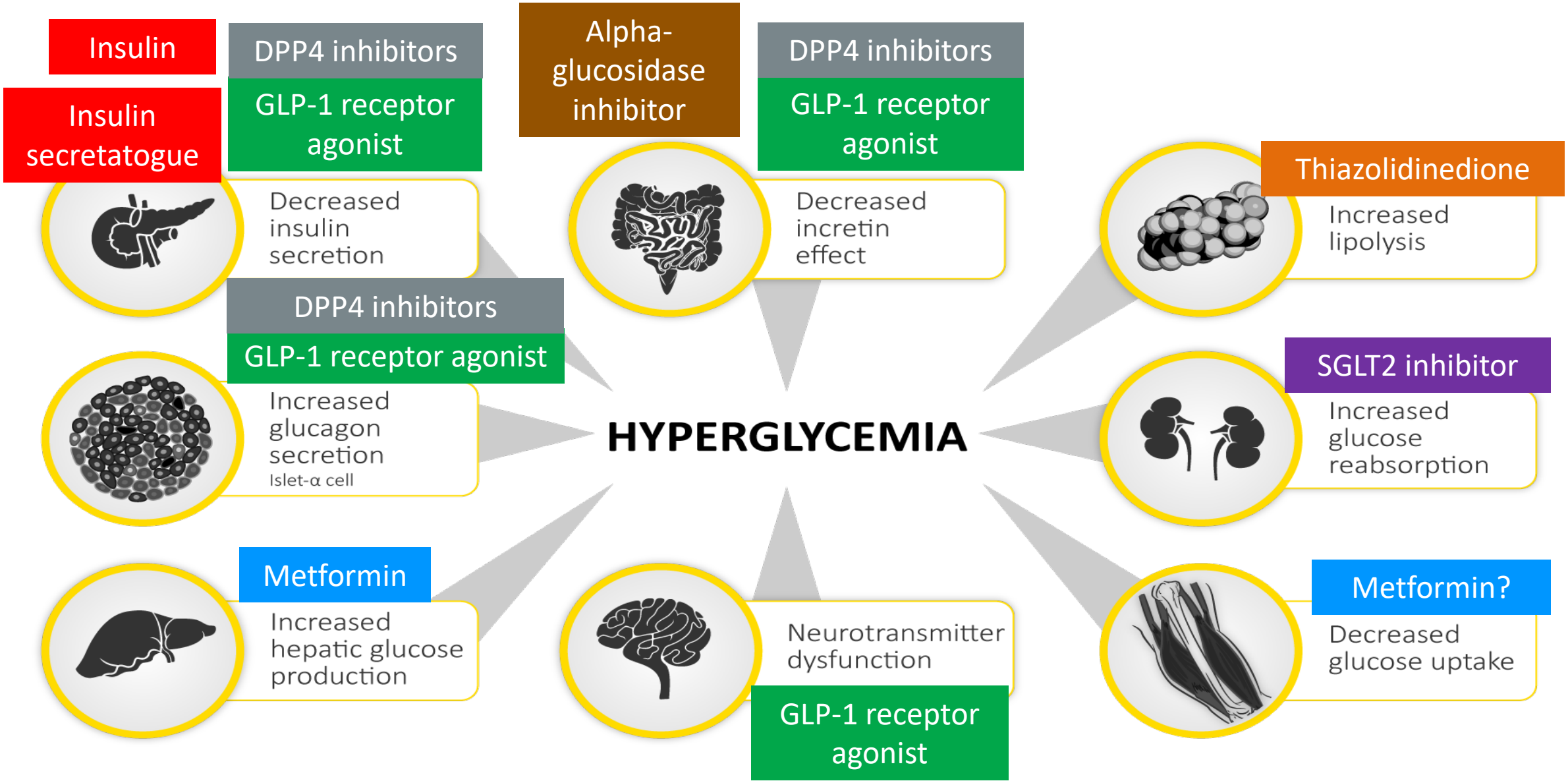
Increasing numbers of acquired risk factors can accelerate trajectory of beta-cell failure and lead to younger age of diagnosis in individuals with similar beta-cell capacity at birth



The more cardiometabolic risk factors which are controlled, the slower the rate of decline in beta-cell function which may delay the need for insulin requirement. On average, 50% of individuals with diabetes may need insulin after 10 years of disease duration especially if control is suboptimal

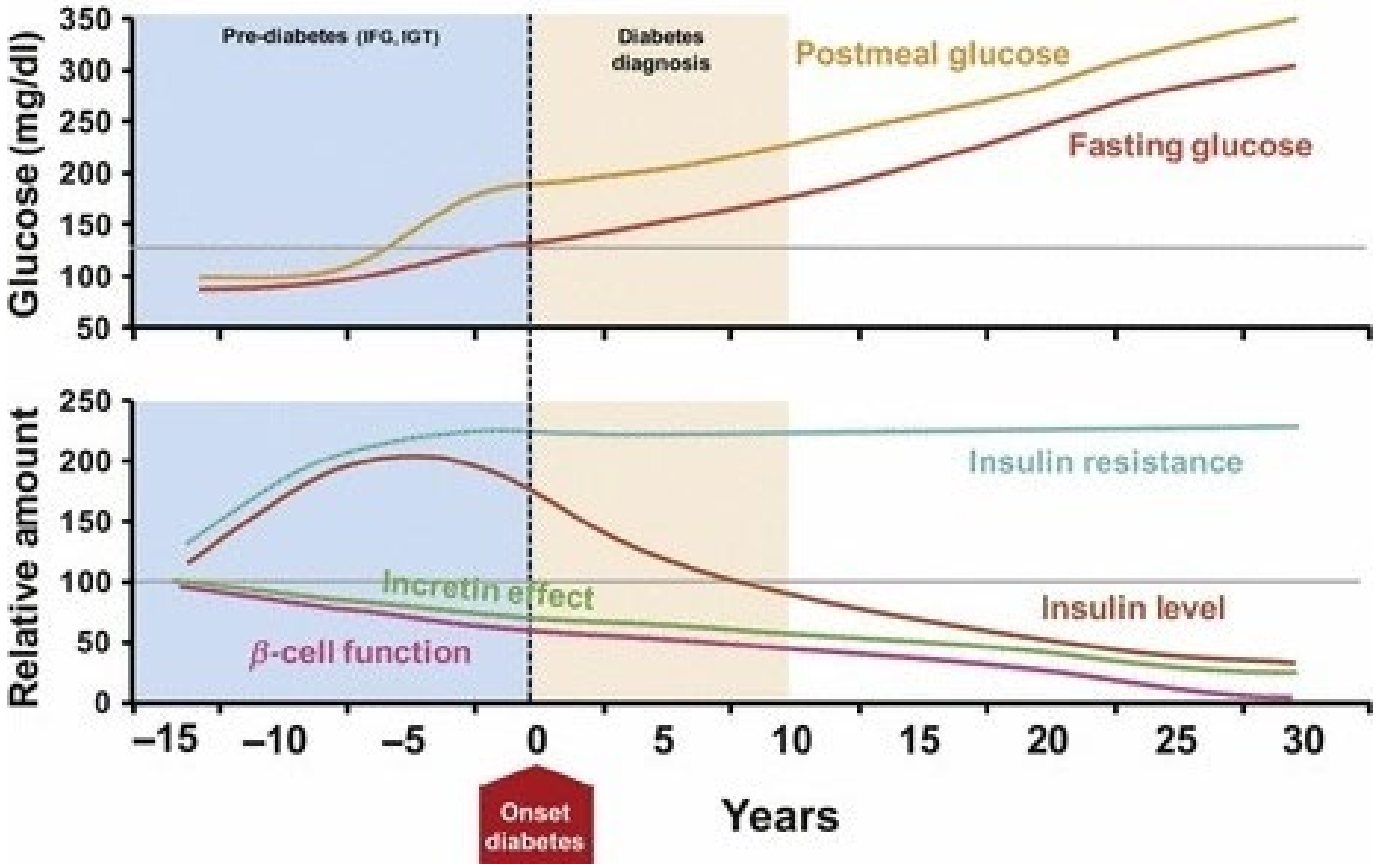


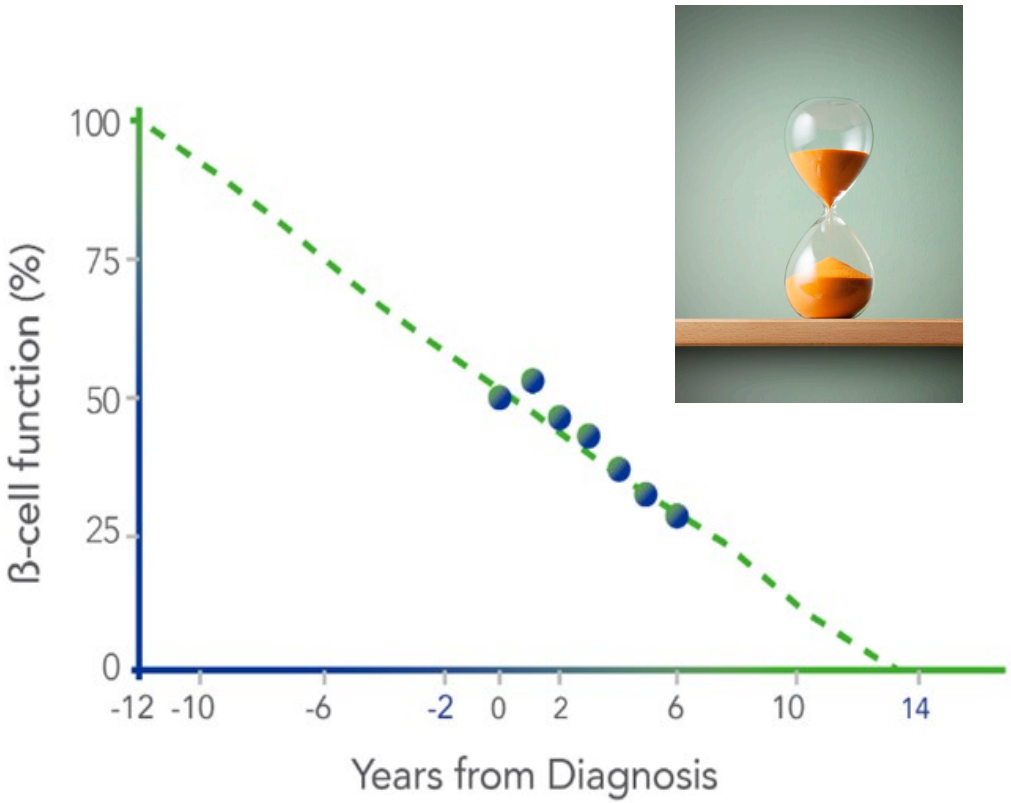
Chan JC et al. J Transl Genet Genom 2024;8:13-34.



Defronzo RA. Diabetes 2009;58(4):773-95.
Abdul-Ghani et al. Diabetes Care 2017;40:1121-1127.

Natural history of type 2 diabetes



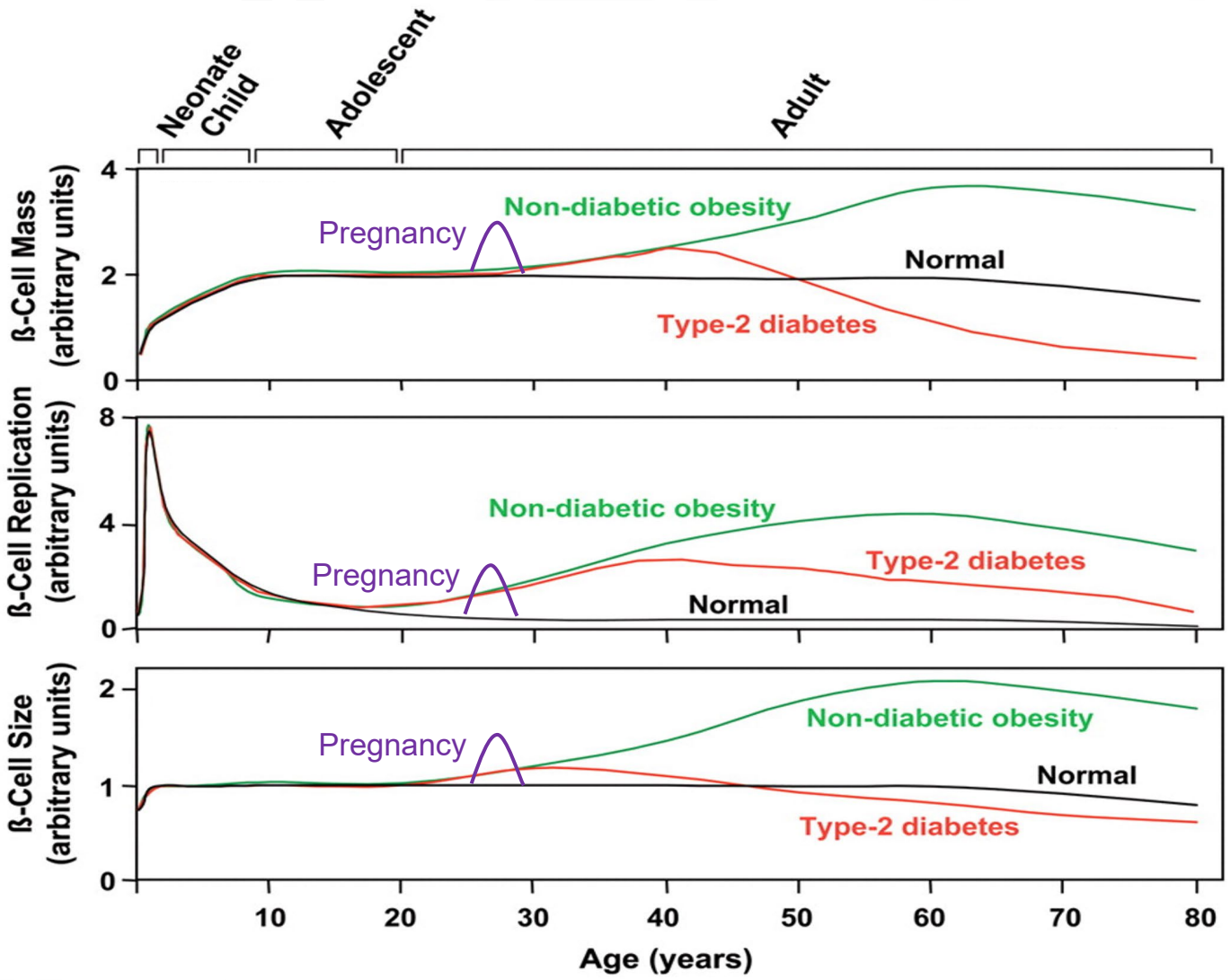


DeFronzo RA. *Diabetes.* 2009;58(4):773-795.

Menin Inhibition and Beta-Cell Biology

Rohit N. Kulkarni, MD, PhD
Joslin Diabetes Center

Beta Cell Compensation in Physiological and Pathophysiological States in Mammals



β-Cell Mass

β-Cell Replication

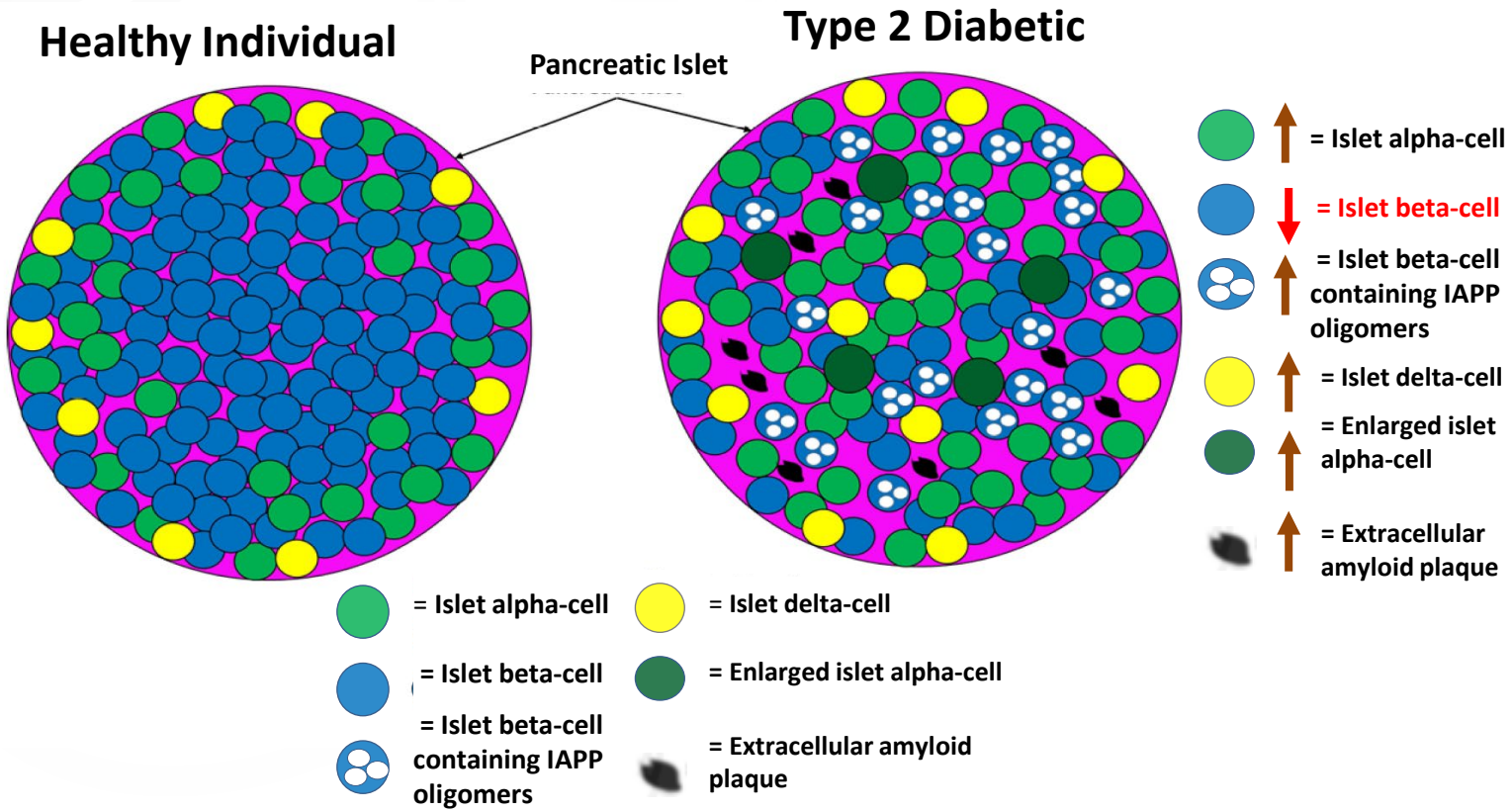
β-Cell Size

Normal Beta Cell Biology

- **97% of the human beta cell pool is established by age 20**
- **Beta cell lifespan in humans is >20-30 yrs**
- **Many (but not all) beta cells remain postmitotic for their lifetime**

Adapted from Science 2005; Cnop M et al. Longevity of human islet alpha- and beta-cells. *Diabetes Obes Metab*. 2011

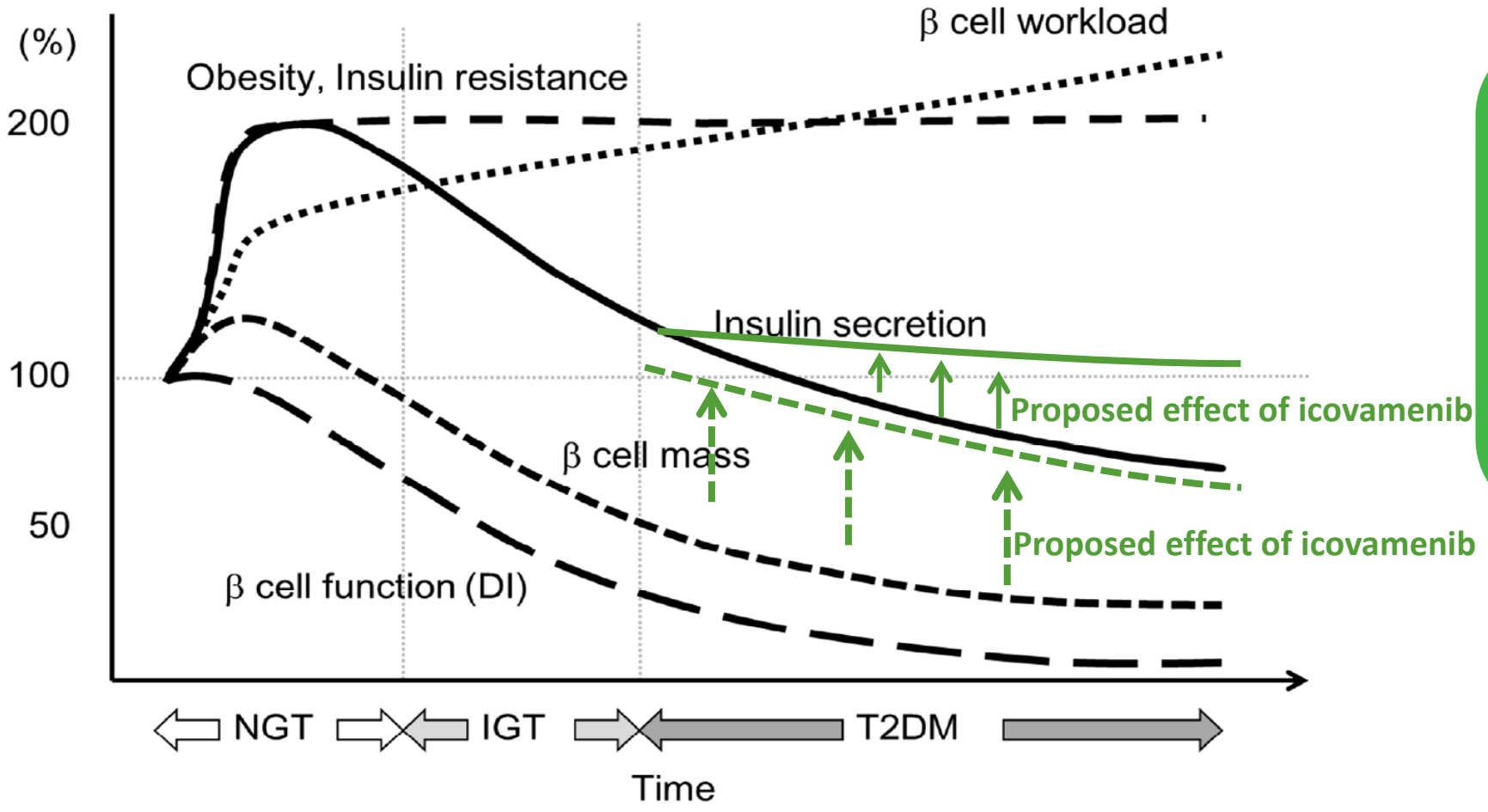
Type 1 and 2 Diabetes Progression Results in Ongoing Beta Cell Loss



- Beta cell mass is decreased by ≥50% at diagnosis in patients with T2D
- Beta cell mass is decreased >90% at diagnosis in patients with T1D
- Glucose remains uncontrolled and beta cell function & number continue to deteriorate in both T1D (autoimmune destruction) and T2D (glucolipotoxicity)
- Standard-of-Care agents do not address the depleted pool of beta cells – the root cause of diabetes

Int. J. Mol. Sci.* **2016, *17*, 744; doi:10.3390/ijms17050744`

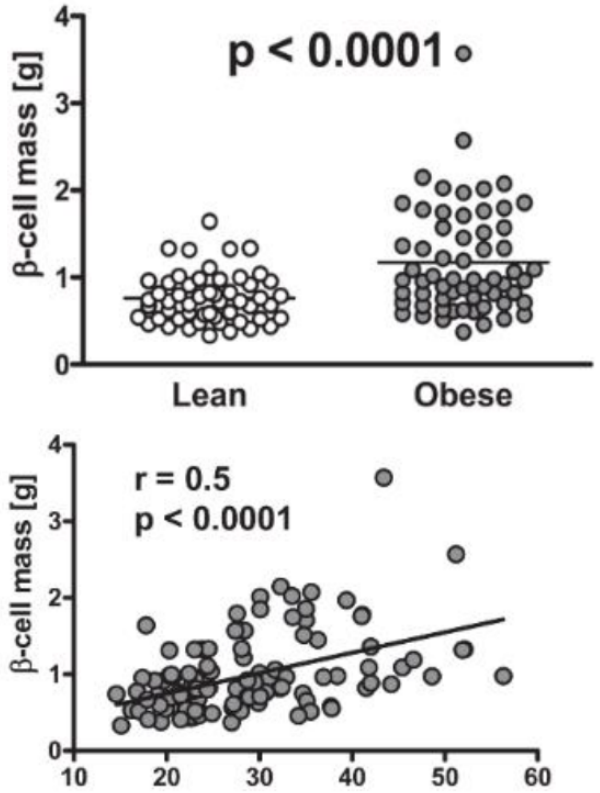
The Goal for icovamenib is to Improve Glycemic Control without Continuous Medication



Biomea's covalent menin inhibitor, icovamenib, is designed to increase the beta cell mass and function, increasing insulin production to achieve glycemic control - without the need for continuous medication

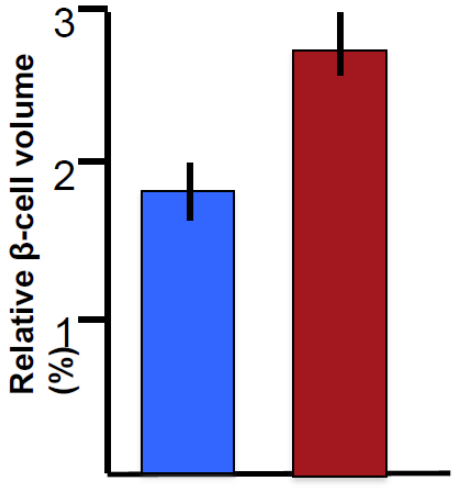
Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744

What Prevents Many Obese Individuals (with Insulin Resistance) from Developing T2D?

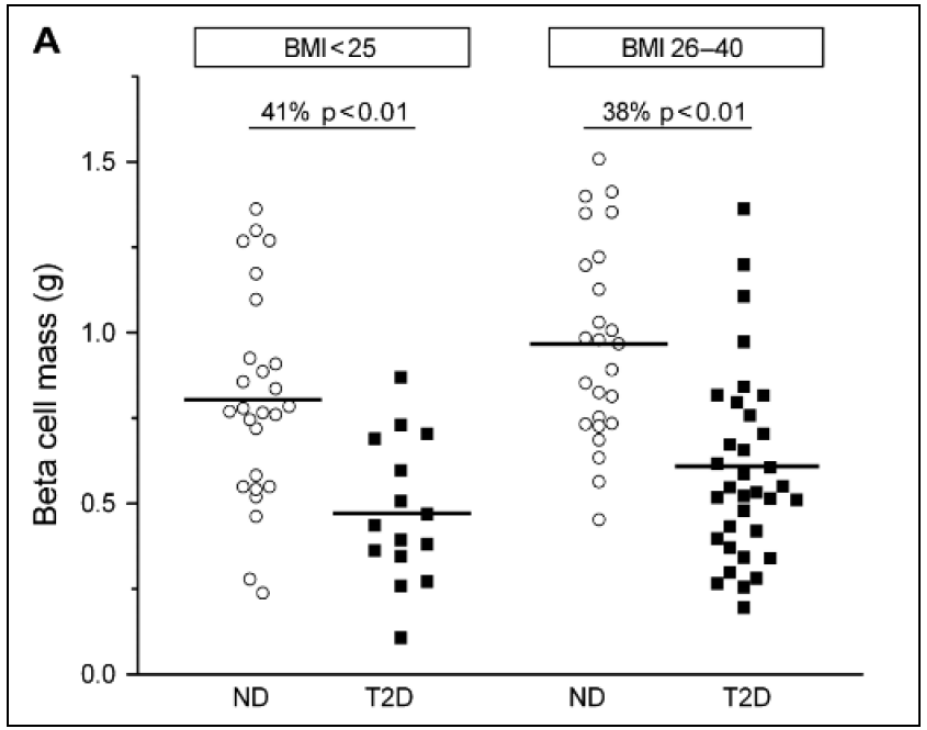


Saisho Y et al, Diabetes care, August 2012

β-cell volume is 20-50% higher in Obese humans without diabetes



Adapted from Butler AE et al. *Diabetes*. 2003;52:102-10.



Rahier et al. Diabetes Obes Metab. 2008 4:32-42

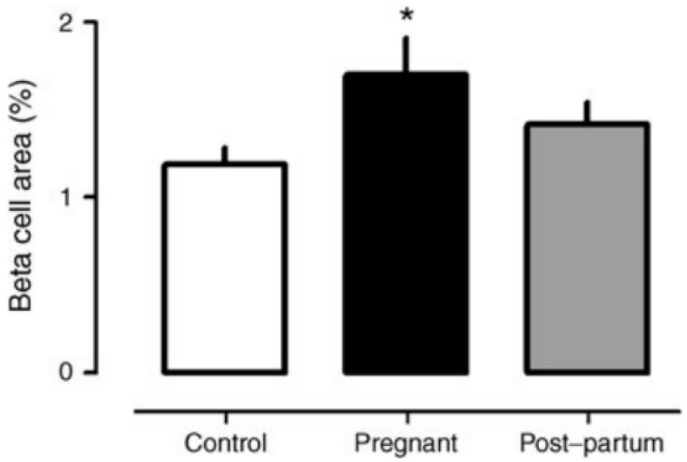
Beta Cells Adapt to the Metabolic Demands in Pregnancy

TABLE II

The endocrine pancreas in non-pregnant and pregnant women

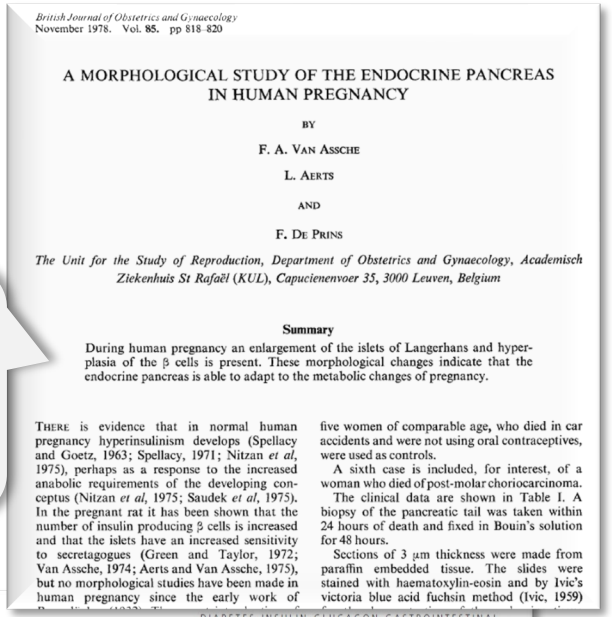
	Endocrine tissue (per cent)	β cells (per cent)
Non-pregnant women		
1	1·6	75
2	1·5	68
3	2·0	78
4	1·4	69
5	1·3	74
Mean ± SD	1·56 ± 0·27	72·8 ± 4·2
Pregnant women		
1	3·2	81
2	3·1	83
3	2·9	79
4	3·6	84
5	3·7	83
Mean ± SD	3·3 ± 0·3	82·0 ± 1·8
P	<0·001	<0·005

Assche and Aerts.
***British Journal of Obstetrics and Gynaecology*. 1978**



Butler et al. Diabetologia. 2010

"This quantitative morphological study shows a **marked enlargement of the islets of Langerhans in pregnant women**."
F. A. Van Assche et al. British Jornal of Obstetrics and Gynaecology, 1978 November



British Journal of Obstetrics and Gynaecology
November 1978. Vol. 85. pp 818–820

A MORPHOLOGICAL STUDY OF THE ENDOCRINE PANCREAS IN HUMAN PREGNANCY

BY

F. A. VAN ASSCHE

L. AERTS

AND

F. DE PRINS

The Unit for the Study of Reproduction, Department of Obstetrics and Gynaecology, Academisch Ziekenhuis St Rafaël (KUL), Capucienenvoer 35, 3000 Leuven, Belgium

Summary

During human pregnancy an enlargement of the islets of Langerhans and hyperplasia of the β cells is present. These morphological changes indicate that the endocrine pancreas is able to adapt to the metabolic changes of pregnancy.

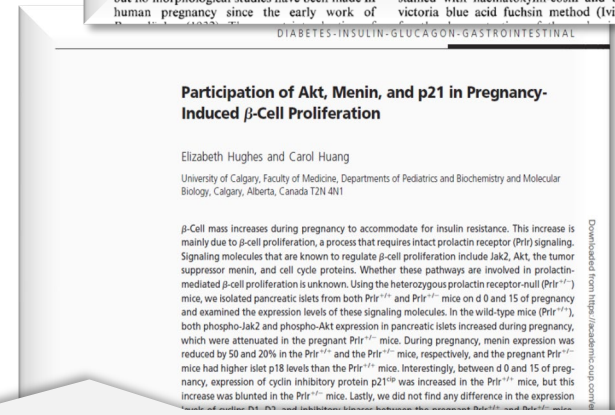
THERE is evidence that in normal human pregnancy hyperinsulinism develops (Spellacy and Goetz, 1963; Spellacy, 1971; Nitzan *et al*, 1975), perhaps as a response to the increased anabolic requirements of the developing conceptus (Nitzan *et al*, 1975; Saudek *et al*, 1975). In the pregnant rat it has been shown that the number of insulin producing β cells is increased and that the islets have an increased sensitivity to secretagogues (Green and Taylor, 1972; Van Assche, 1974; Aerts and Van Assche, 1975), but no morphological studies have been made in human pregnancy since the early work of

five women of comparable age, who died in car accidents and were not using oral contraceptives, were used as controls.

A sixth case is included, for interest, of a woman who died of post-molar choriocarcinoma.

The clinical data are shown in Table I. A biopsy of the pancreatic tail was taken within 24 hours of death and fixed in Bouin's solution for 48 hours.

Sections of 3 μm thickness were made from paraffin embedded tissue. The slides were stained with haematoxylin-eosin and by Ivic's victoria blue acid fuchsin method (Ivic, 1959)



DIABETES-INSULIN-GLUCAGON-GASTROINTESTINAL

Participation of Akt, Menin, and p21 in Pregnancy-Induced β-Cell Proliferation

Elizabeth Hughes and Carol Huang

University of Calgary, Faculty of Medicine, Departments of Pediatrics and Biochemistry and Molecular Biology, Calgary, Alberta, Canada T2N 4N1

β-Cell mass increases during pregnancy to accommodate for insulin resistance. This increase is mainly due to β-cell proliferation, a process that requires intact prolactin receptor (Prlr) signaling. Signaling molecules that are known to regulate β-cell proliferation include Jak2, Akt, the tumor suppressor menin, and cell cycle proteins. Whether these pathways are involved in prolactin-mediated β-cell proliferation is unknown. Using the heterozygous prolactin receptor-null ($Prlr^{+/-}$) mice, we isolated pancreatic islets from both $Prlr^{+/+}$ and $Prlr^{+/-}$ mice on d 0 and 15 of pregnancy and examined the expression levels of these signaling molecules. In the wild-type mice ($Prlr^{+/+}$), both phospho-Jak2 and phospho-Akt expression in pancreatic islets increased during pregnancy, which were attenuated in the pregnant $Prlr^{+/-}$ mice. During pregnancy, menin expression was reduced by 50 and 20% in the $Prlr^{+/+}$ and the $Prlr^{+/-}$ mice, respectively, and the pregnant $Prlr^{+/-}$ mice had higher islet p18 levels than the $Prlr^{+/+}$ mice. Interestingly, between d 0 and 15 of pregnancy, expression of cyclin inhibitory protein $p21^{CIP}$ was increased in the $Prlr^{+/+}$ mice, but this increase was blunted in the $Prlr^{+/-}$ mice. Lastly, we did not find any difference in the expression

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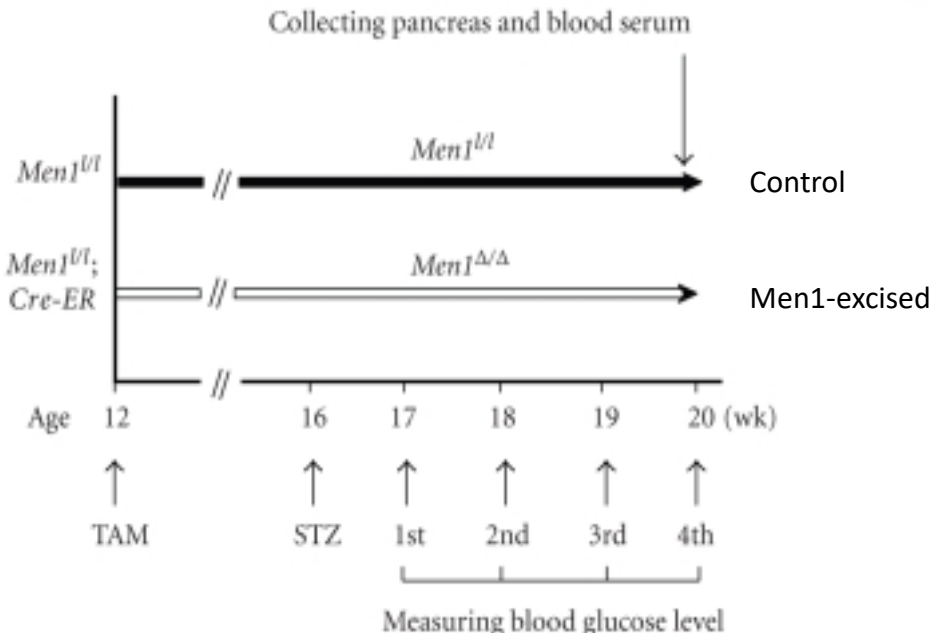
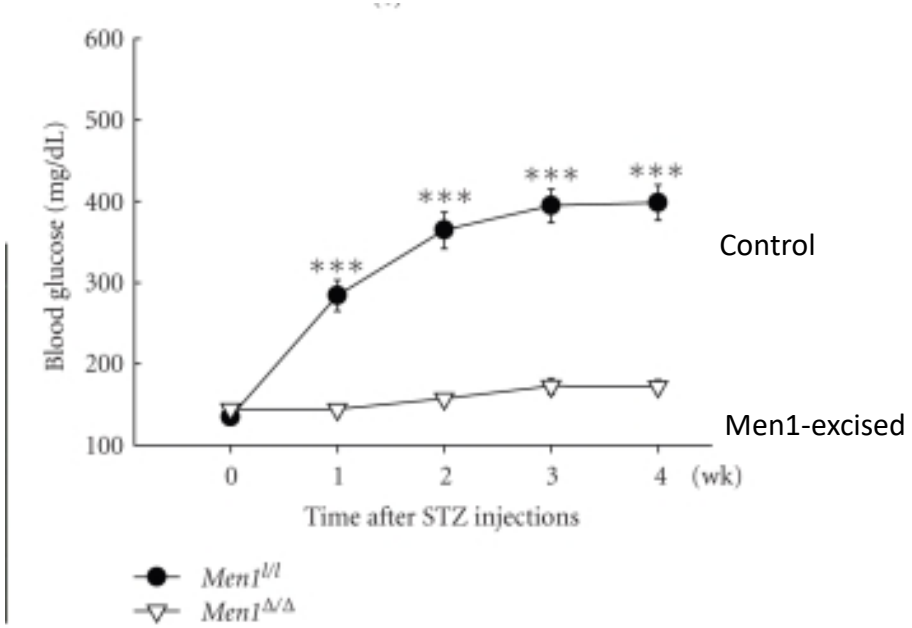
"We conclude that **during pregnancy**, placental hormones act through the prolactin receptor to increase beta cell mass by **up regulating beta cell proliferation** by engaging Jak2, Akt, **menin**/p18, and p21."
Hughs et al. Endocrinology, March 2011, 152(3):847–855

Potential for Menin Inhibition Demonstrated by Beta Cell Ablation Diabetes Model in MEN1-Excised Mice

MEN1 Excision Prevents Development of STZ-induced Hyperglycemia



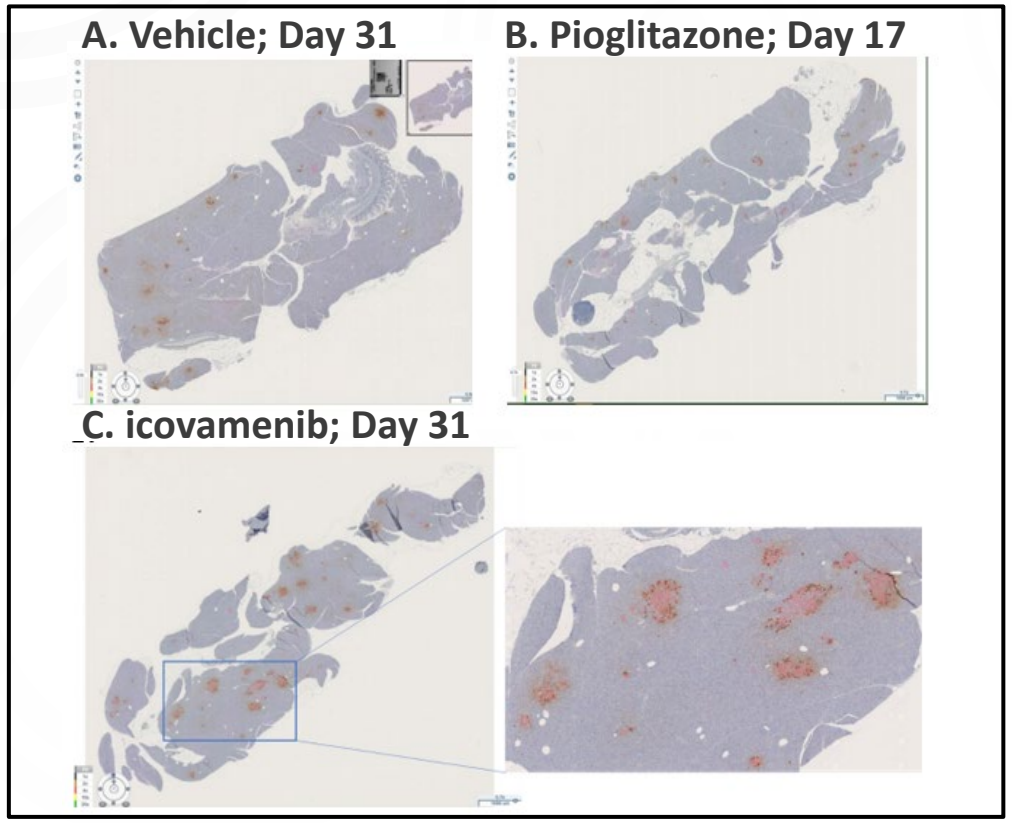
Multiple low-dose streptozotocin (MLD-STZ) administered to the control and *Men1*-excised mice to induce beta cell damage and a diabetes-like environment



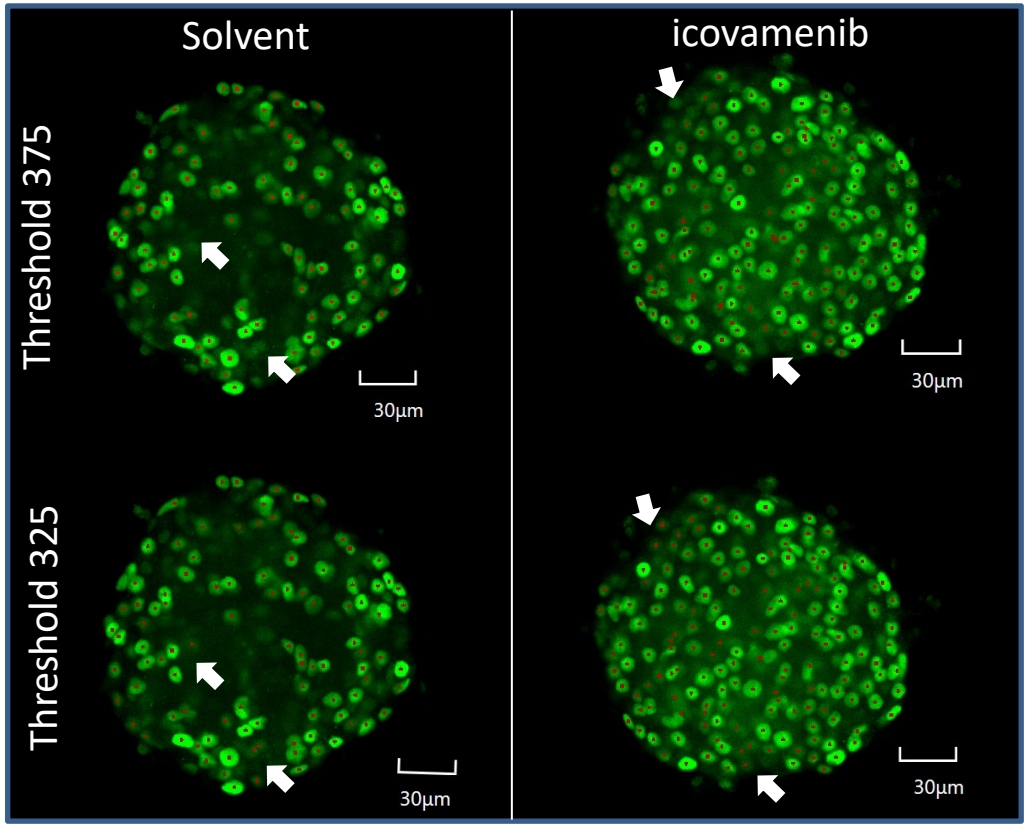
***Men1*-excised mice did not develop hyperglycemia in STZ model, which was observed in the control group**

Sources: Yang et al. (2010) Deletion of theMen1Gene Prevents Streptozotocin-Induced Hyperglycemia in Mice. Experimental Diabetes Research, 2010, 1–11. doi:10.1155/2010/876701

Icovamenib Increases Beta-Cell Mass in Both in Vivo Rodent Models and ex Vivo Human Islets



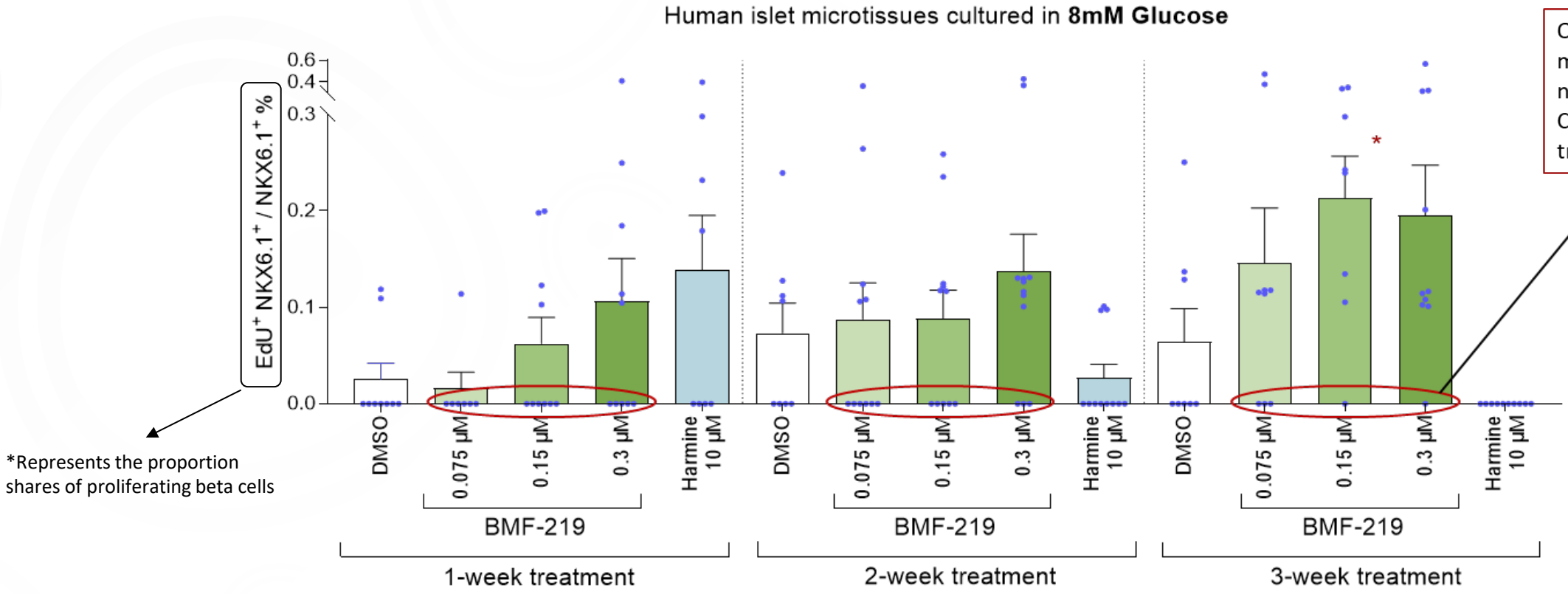
ZDF Diabetic Model: A) Vehicle-treated animal, Day 31. Beta islets display low congregation and growth, while alpha cells dominate. B) Pioglitzaone-treated animal, Day 17. Beta islets display congregation and growth. C) Icovamenib treated animal, Day 31. Beta islets display high congregation and continue to increase and mature. Red is insulin-beta islets, brown is glucagon-alpha cells.



Human Donor Islets (Ex Vivo): Statistically significant increase in beta cells with icovamenib

Longer Dosing is Predicted to Generate an Increase in Responder Rates Based on Human Donor Islet Experiments

Proliferating beta cells plotted as fraction of total beta cells



Over time, fewer islet microtissues remain, that do not have proliferating β-cells. Compare 1, 2 and 3 weeks treatment duration.

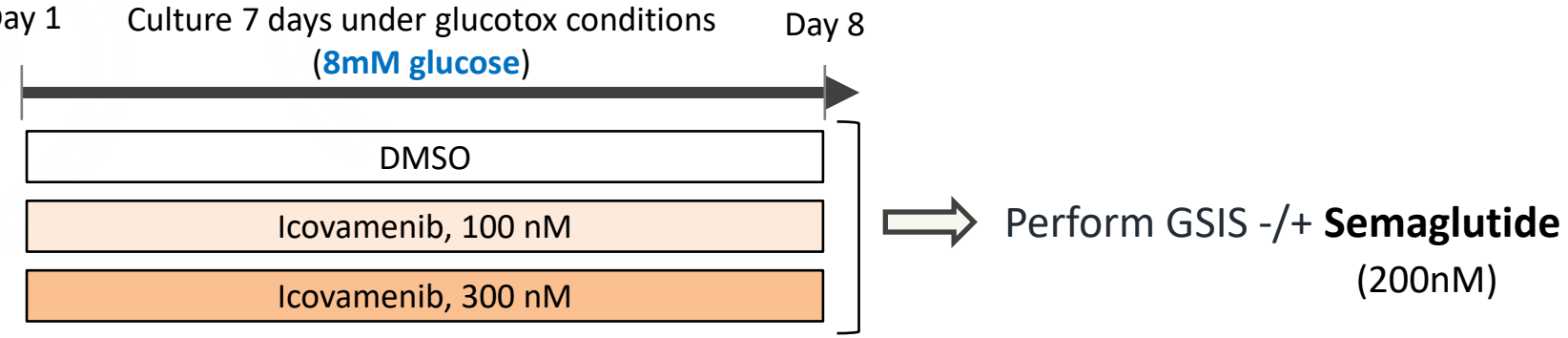
*Represents the proportion shares of proliferating beta cells

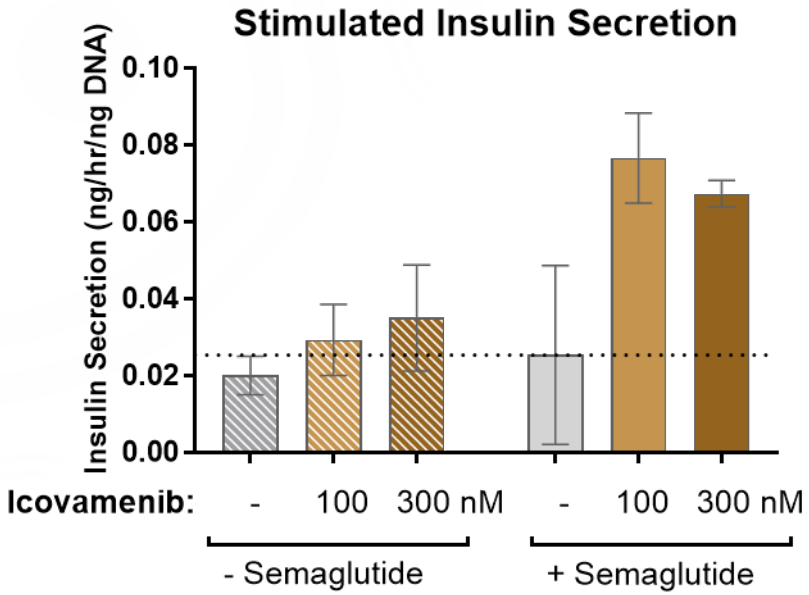
Data represent mean ±SEM of 1 donor with n = 9-12 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

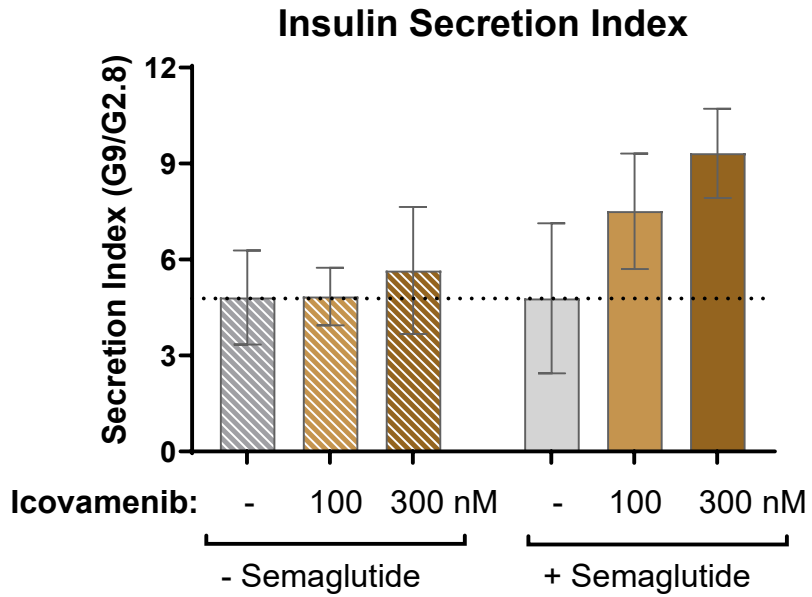
Combination Treatment:
Icovamenib Enhanced Responsiveness of Islets to the GLP-1 RA Semaglutide

Cadaver derived human islets

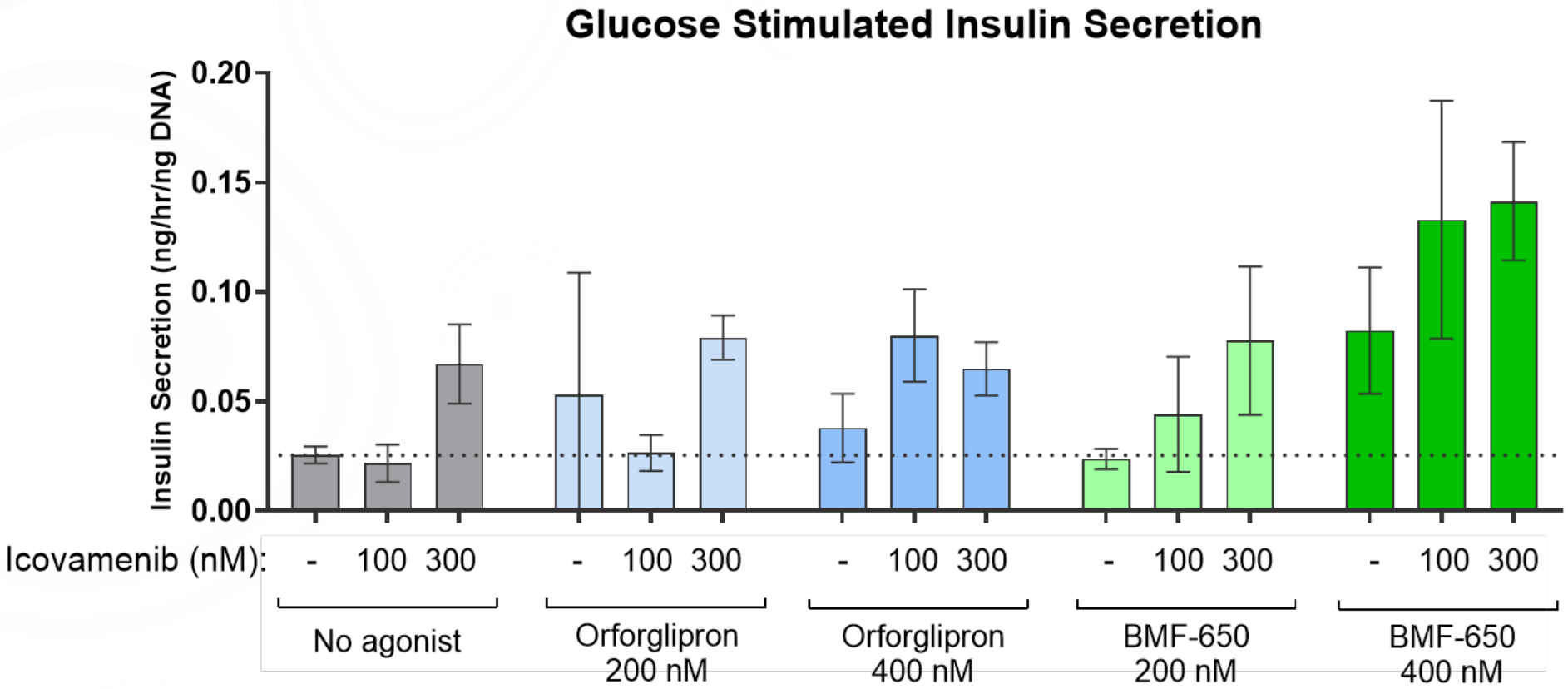
Non-diabetic donor:
41yr Hispanic male, BMI 27.8, HbA1c 5.3%



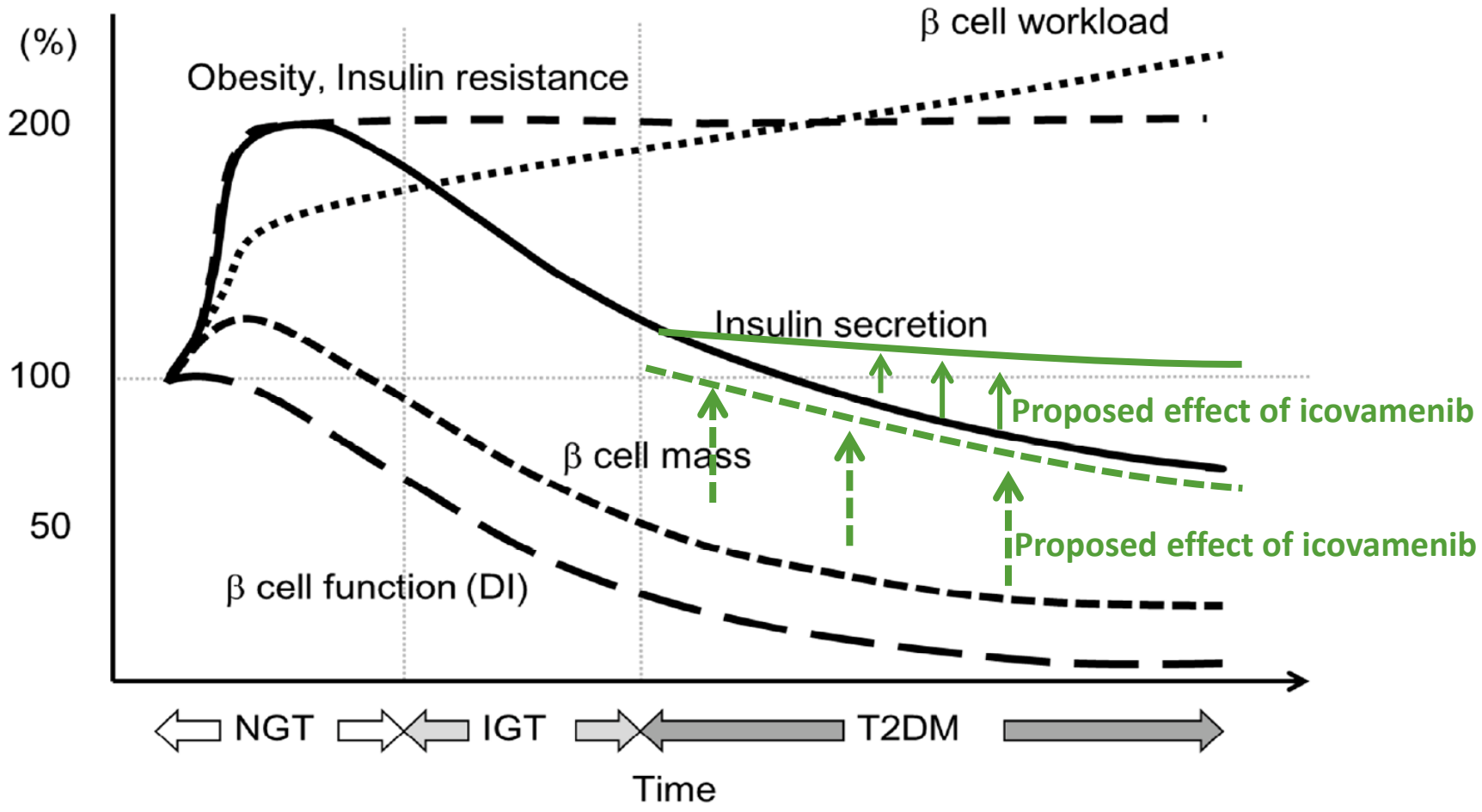




Combination Treatment:
Icovamenib Enhanced Responsiveness of Islets to Small Molecule GLP-1 RAs Orforglipron and BMF-650



The Goal for icovamenib is to Improve Glycemic Control without Continuous Medication



Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744

Key eligibility criteria and study design (Multiple Ascending Dose Cohort)

Eligibility Criteria

- T2D, age 18-65 yr
- Duration of diabetes 15 yr or less
- HbA_{1c} 7.0 to 10.0%
- BMI 25 to 40 kg/m^2
- Treated with diet/exercise ± up to 3 antihyperglycemic agents (insulin secretagogues and insulin excluded)

Primary Objective

- Safety and tolerability of icovamenib

Key Secondary Objectives

- Impact on glycemic parameters
- Changes in beta-cell function
- PK exposure of Icovamenib

COVALENT-111 T2D MAD Cohorts

50 mg QD, without food
x 4 weeks

100 mg QD, without food
x 4 weeks

100 mg QD, with food
x 4 weeks

200 mg QD, without food
x 4 weeks

200 mg QD, with food
x 4 weeks

Icovamenib (n=10) and placebo (n=2) per cohort*

*200 mg with food cohort enrolled n=2 participants

100 mg BID, without food
x 4 weeks

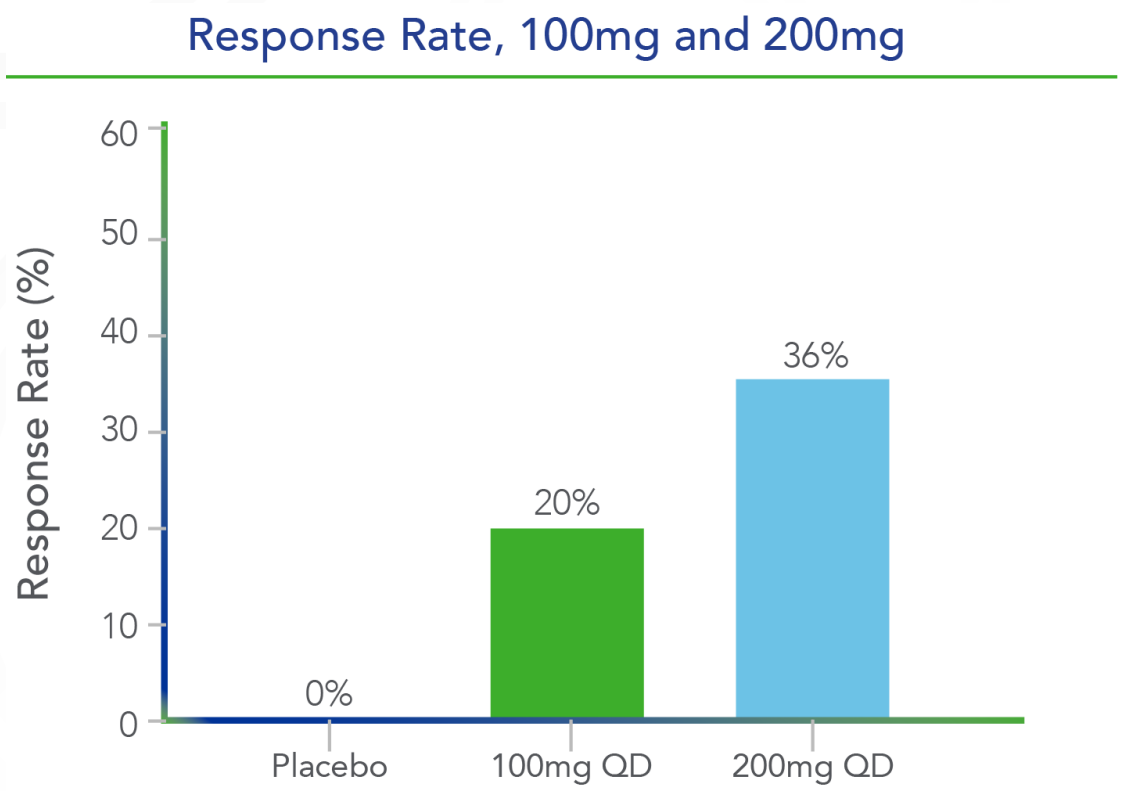
200 mg QD x 2 weeks	**400 mg QD** x 2 weeks

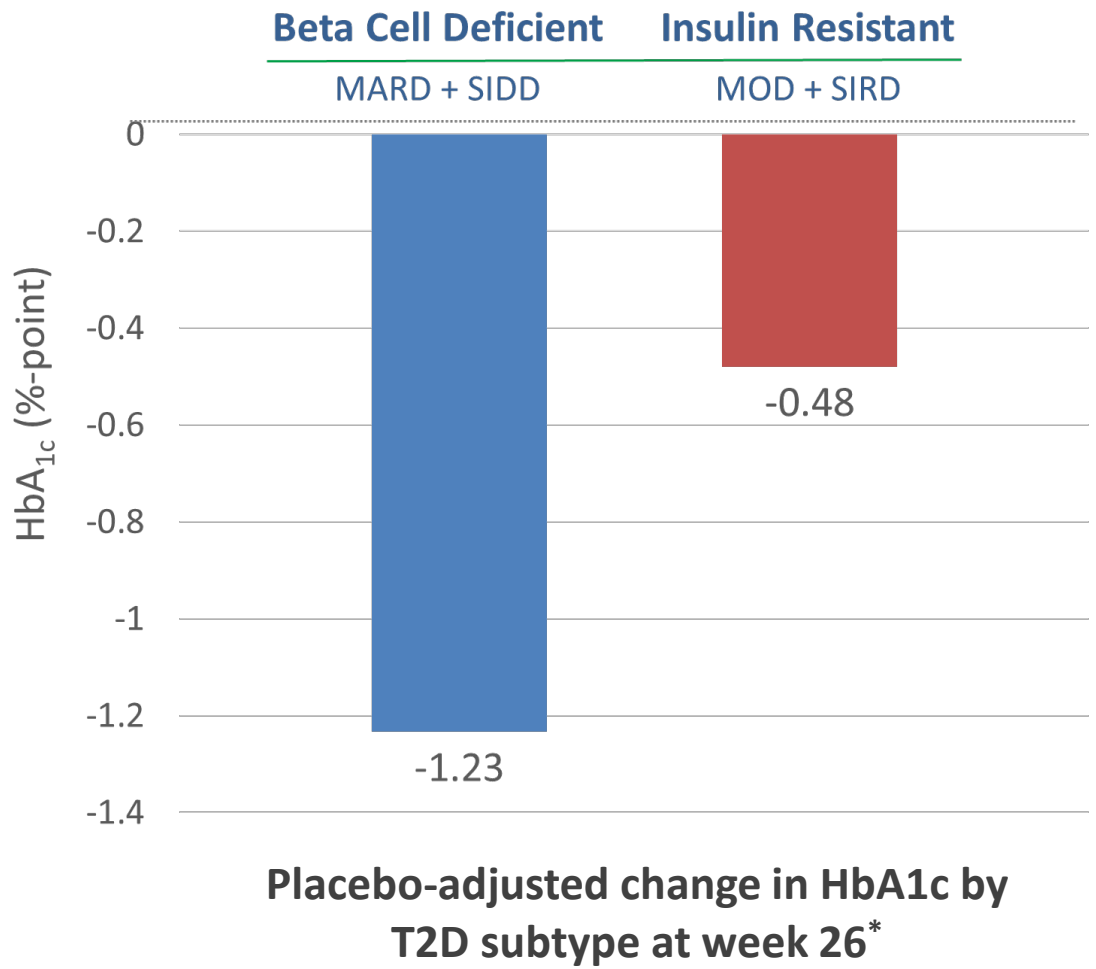
without food

4 weeks dosing + 22 weeks follow-up

https://clinicaltrials.gov/study/NCT05731544

Proportion of patients with ≥1.0% HbA_{1c} reduction at Week 26 and change in HbA1c by T2D subtype





Placebo-adjusted change in HbA1c by T2D subtype at week 26*

Abitbol A, et al. (ATTD 2024, March 6, 2024)
Frías JP, et al. (ATTD-Asia 2024, November 19, 2024)
Subtyping per Ahlqvist E, et al. Lancet Diabetes Endocrinol. 2018;6:361-369

*Includes Cohorts 2, 3, 4 & 7 (100mg QD/BID and 200mg QD, cohorts representative of exposure expected in Expansion Phase, Arms A-C)
MARD/SIDD, N=6; MOD/SIRD N=26

Q & A Session

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