

# Unlocking the Potential of Menin Inhibition

Icovamenib and a Look into the Future of Diabetes Management

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**Juan Pablo Frías, MD**

Chief Medical Officer  
Biomea Fusion, Inc.

**Alice YY Cheng, MD, FRCPC**

Associate Professor of Medicine  
University of Toronto

**Rohit N. Kulkarni, MD, PhD**

Professor of Medicine  
Joslin Clinic, Harvard Medical School

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

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# Introduction to Biomea Fusion and Icovamenib

**Juan Pablo Frías, MD**

Chief Medical Officer and Head of Diabetes  
Biomea Fusion



We Aim to Cure™

# A long history of developing successful drugs - together



**Thomas Butler**  
Chairman & CEO



**Ramses Erdtmann**  
President & COO



**Juan Frías, M.D.**  
Chief Medical Officer



**Naomi Cretcher**  
Chief of People



**Heow Tan**  
Chief Technical & Quality Officer



**Steve Morris, M.D.**  
Chief Development Officer



**Franco Valle**  
Chief Financial Officer



Co-Founder

The **FUSION™ SYSTEM**  
**icovamenib\***  
Co-Inventor



Co-Inventor

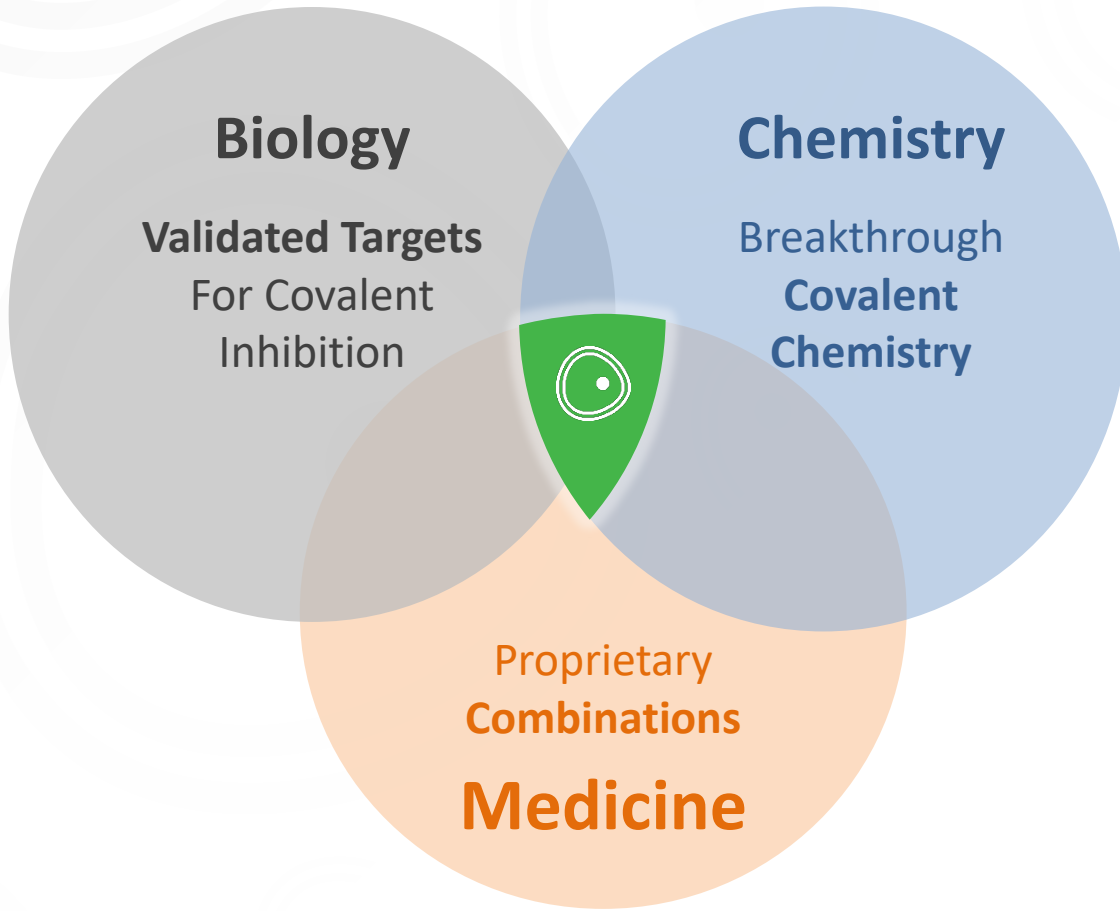


Co-Founder



\*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

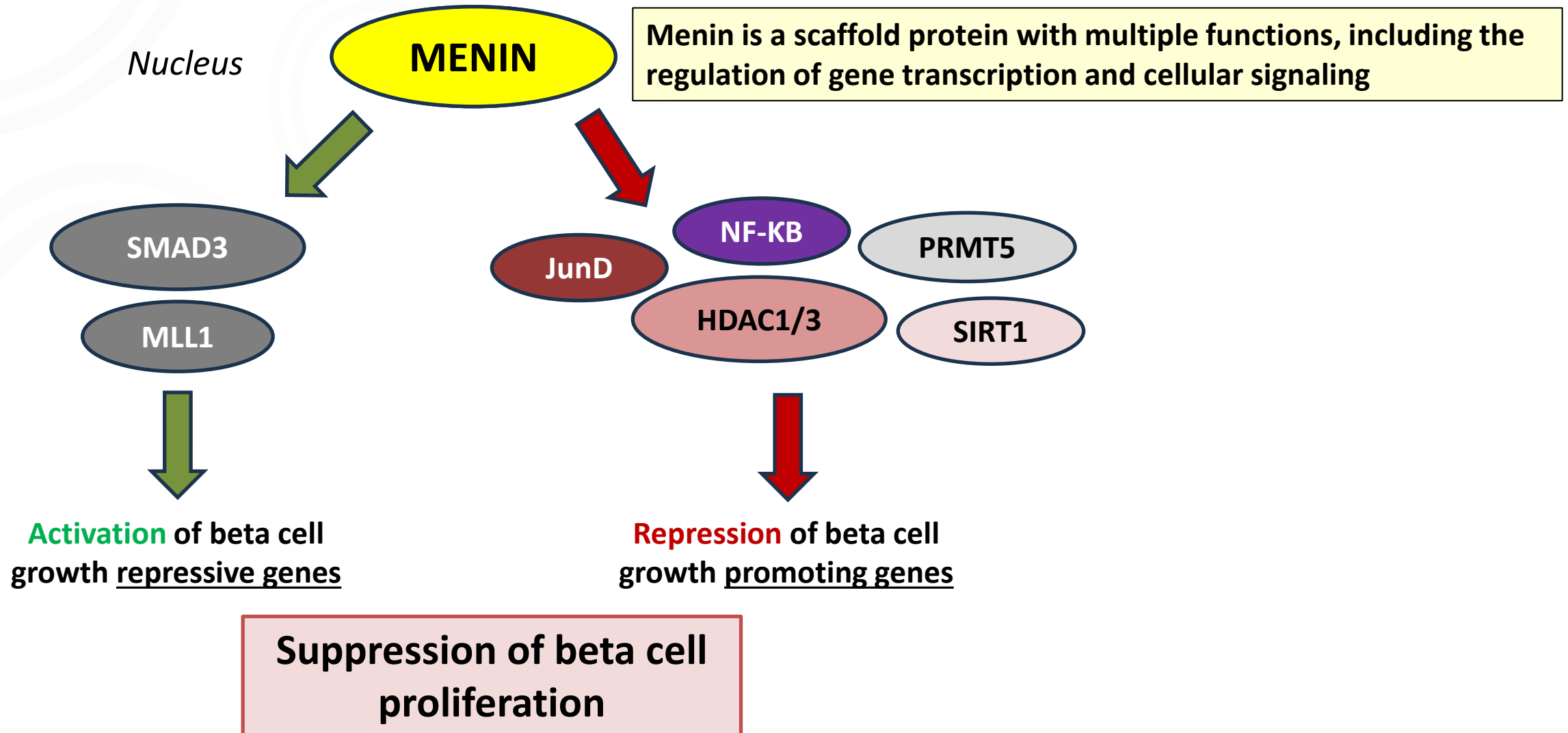
**Combination Therapy** with non-overlapping resistance mechanisms results in more durable responses and better outcomes

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



# Menin's role in beta cell proliferation and glucose homeostasis

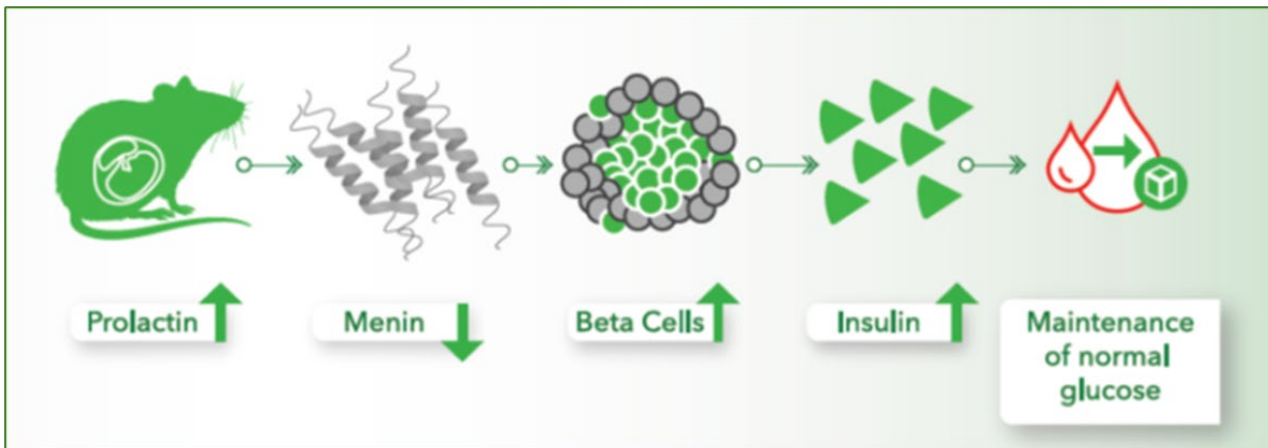
Menin's role in nuclear complexes regulate beta cell proliferation





## 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

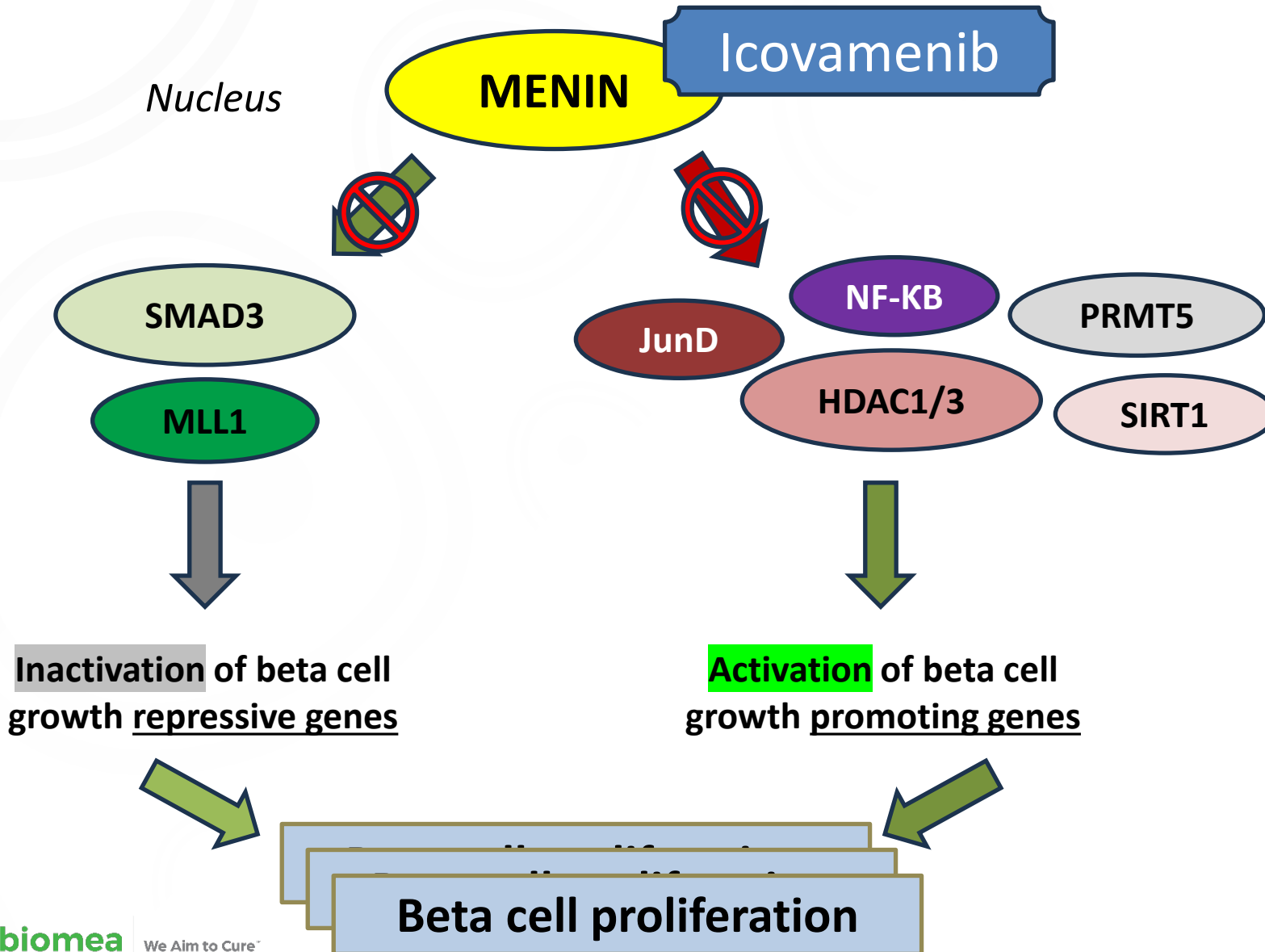
## Menin Controls Growth of Pancreatic $\beta$ -Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

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

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  $\beta$ -cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal  $\beta$ -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  $\beta$ -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:

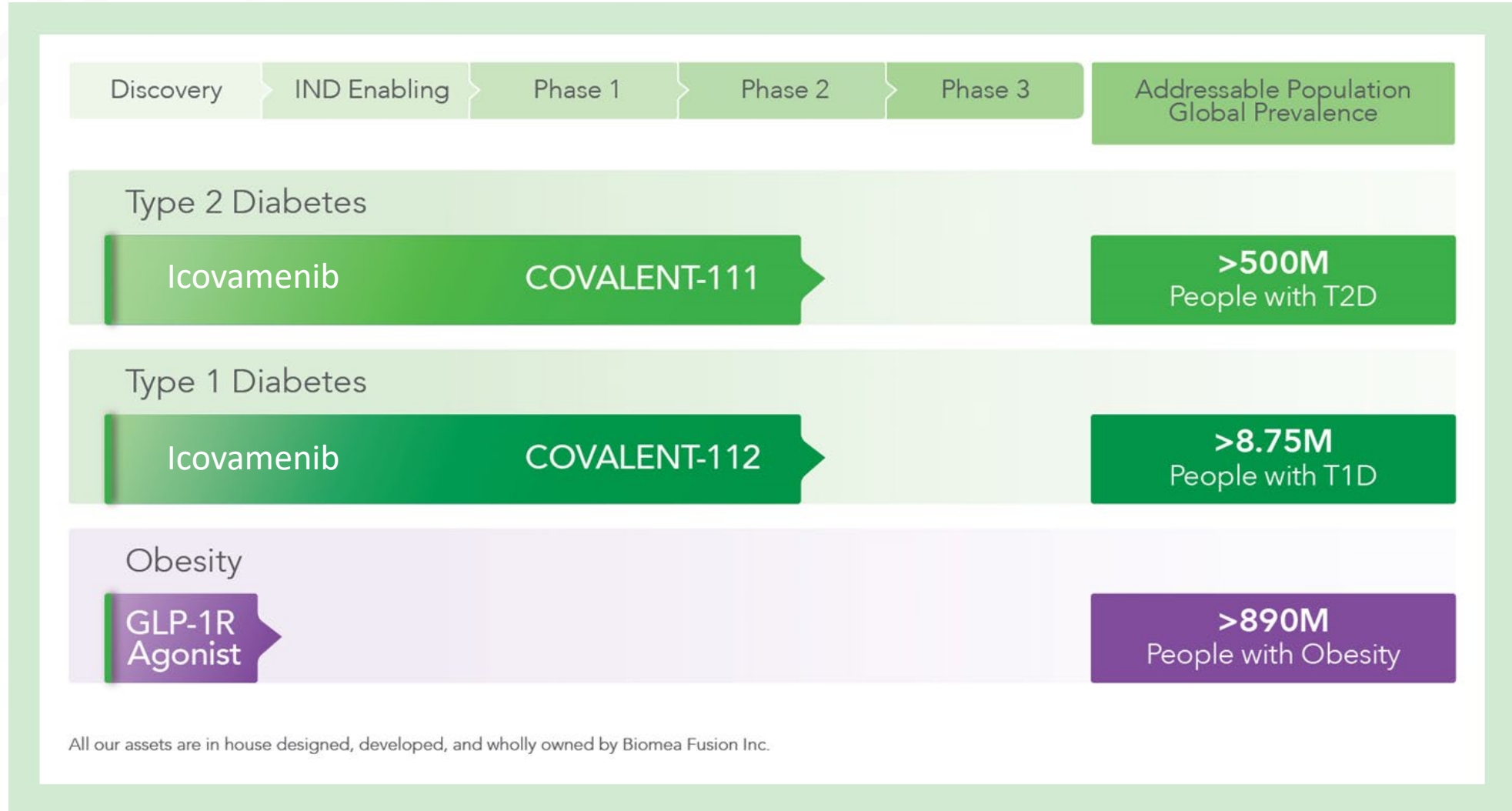
- Short-term icovamenib treatment in diabetic rat models (ZDF and STZ)
- Result: Durable glycemic control observed<sup>1,2</sup>

## Clinical Evidence:

- 4-week daily icovamenib treatment
  - Improved glycemic control at Week 26 (22 wks post-treatment)
  - Generally safe and well-tolerated<sup>3</sup>

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

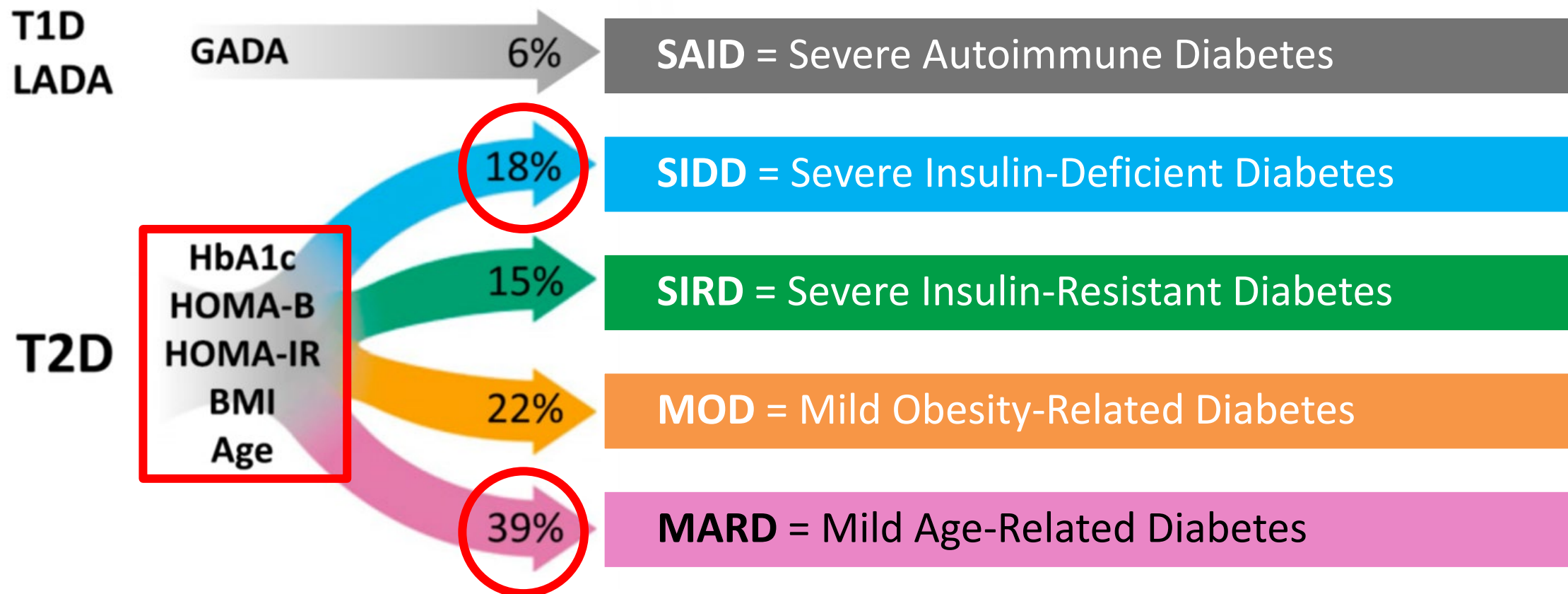
Well-Tolerated Profile  
To Date

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.”<sup>1,2</sup>



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

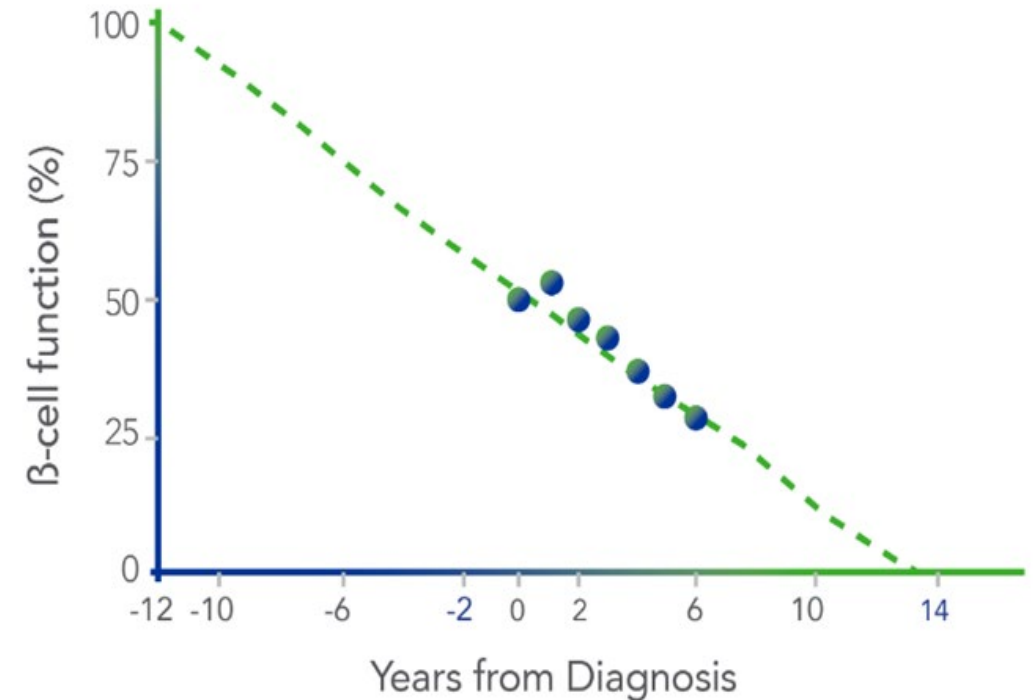
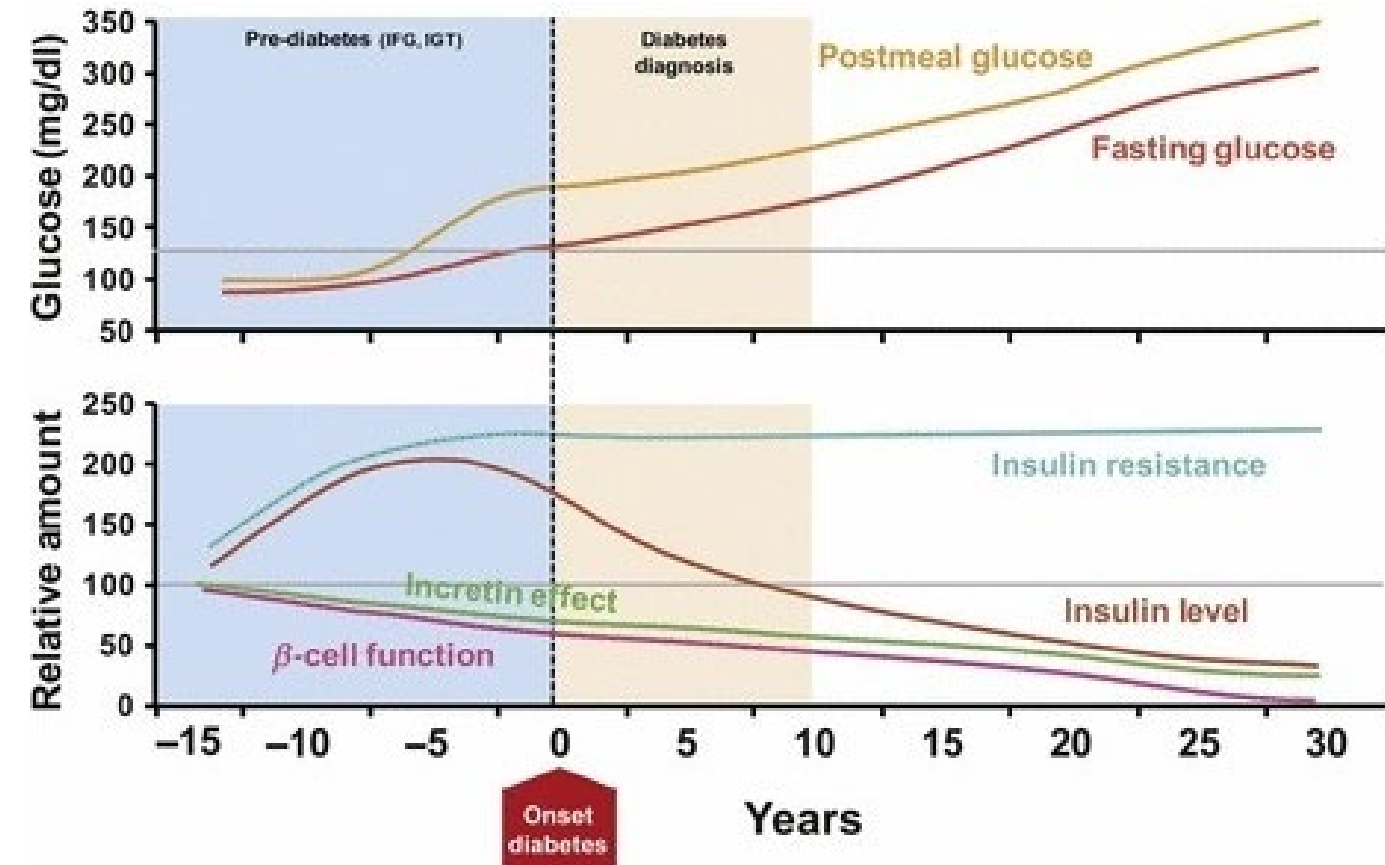


# Disclosures (Alice Cheng)

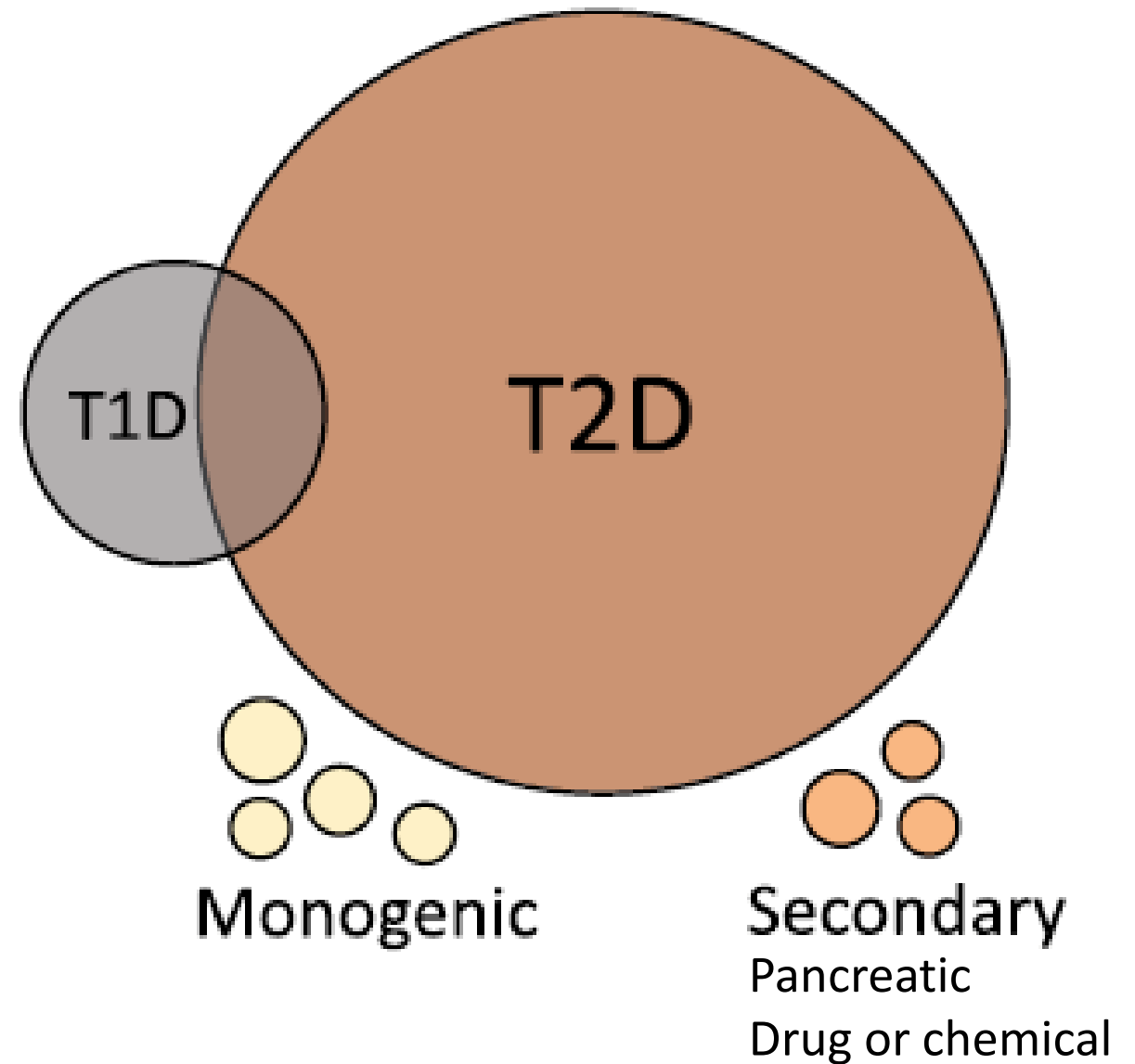
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- **Clinical trial:** Sanofi, Novo Nordisk, Applied Therapeutics



# Natural history of type 2 diabetes



Remember  
When...?





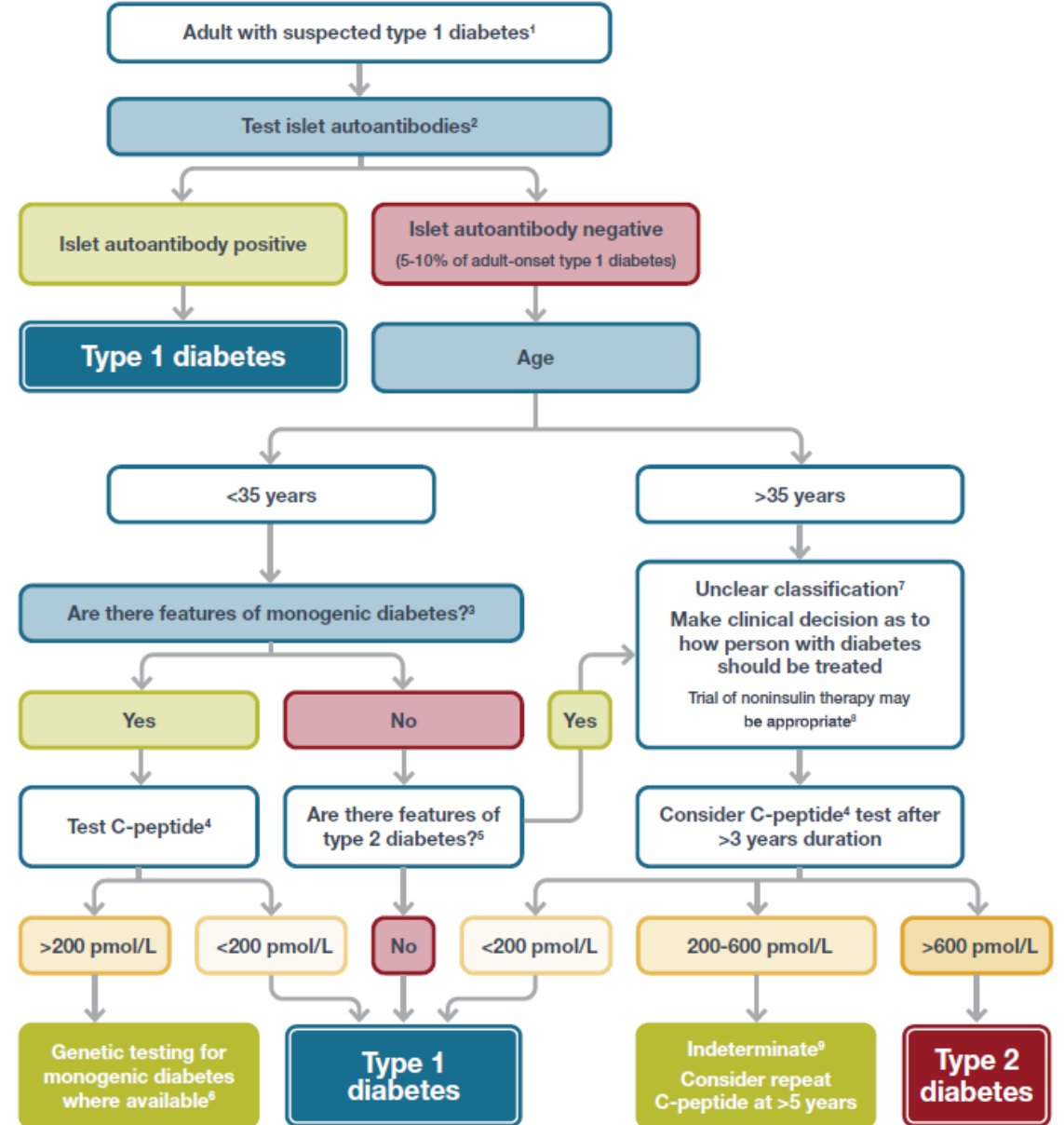
# Diabetes Care

JANUARY 2024 | VOLUME 47 | SUPPLEMENT 1

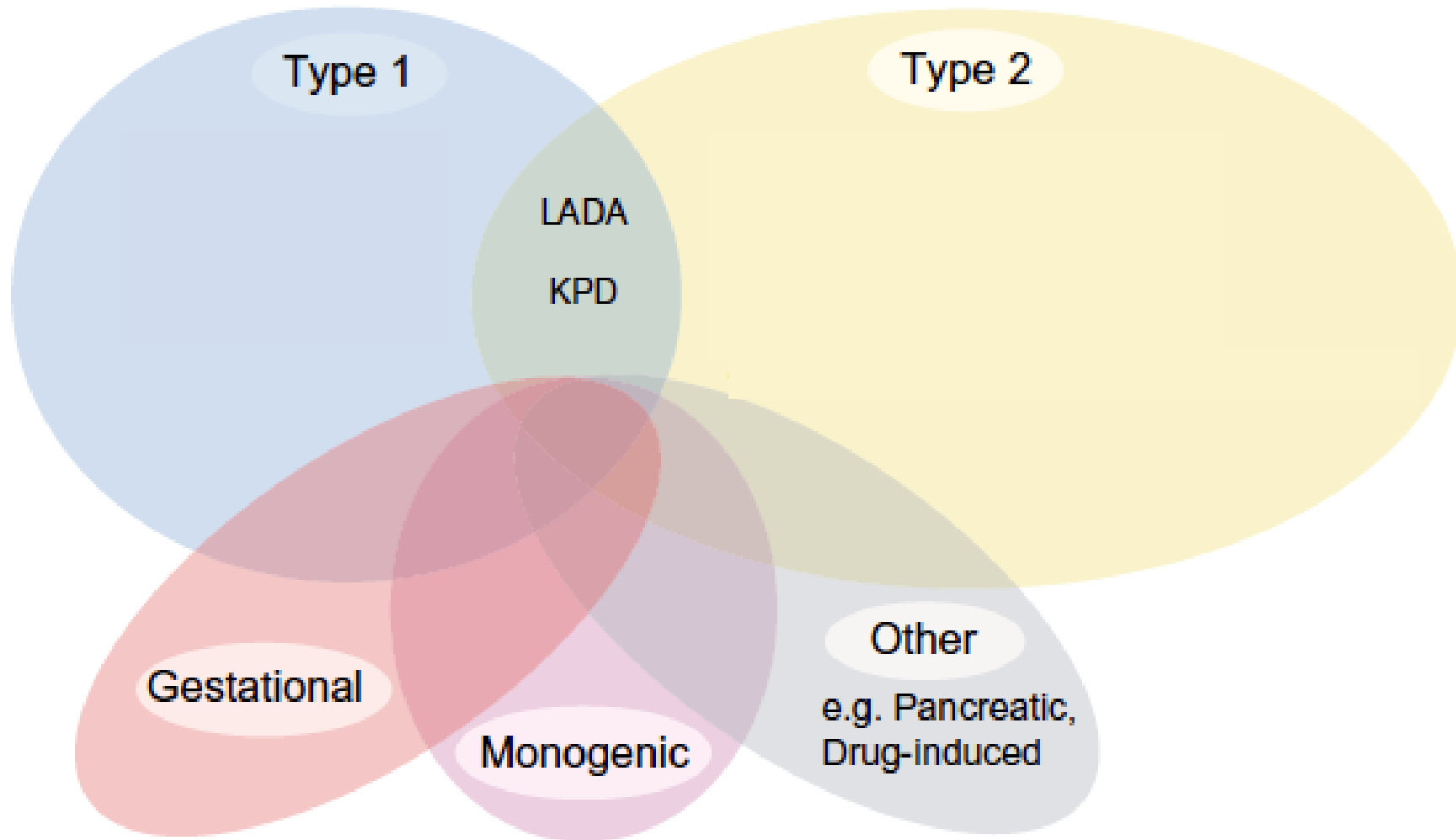
WWW.DIABETESJOURNALS.ORG/CARE

## Standards of Care in Diabetes—2024

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



# 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\*, Mozghan 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*

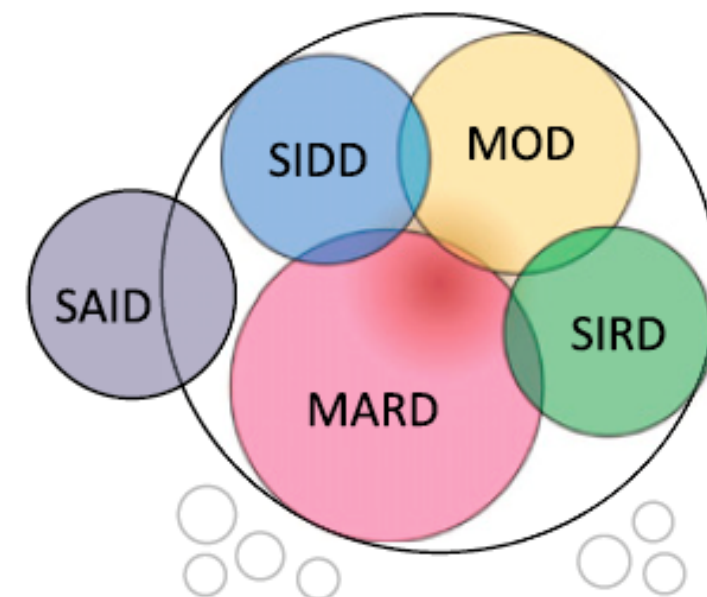
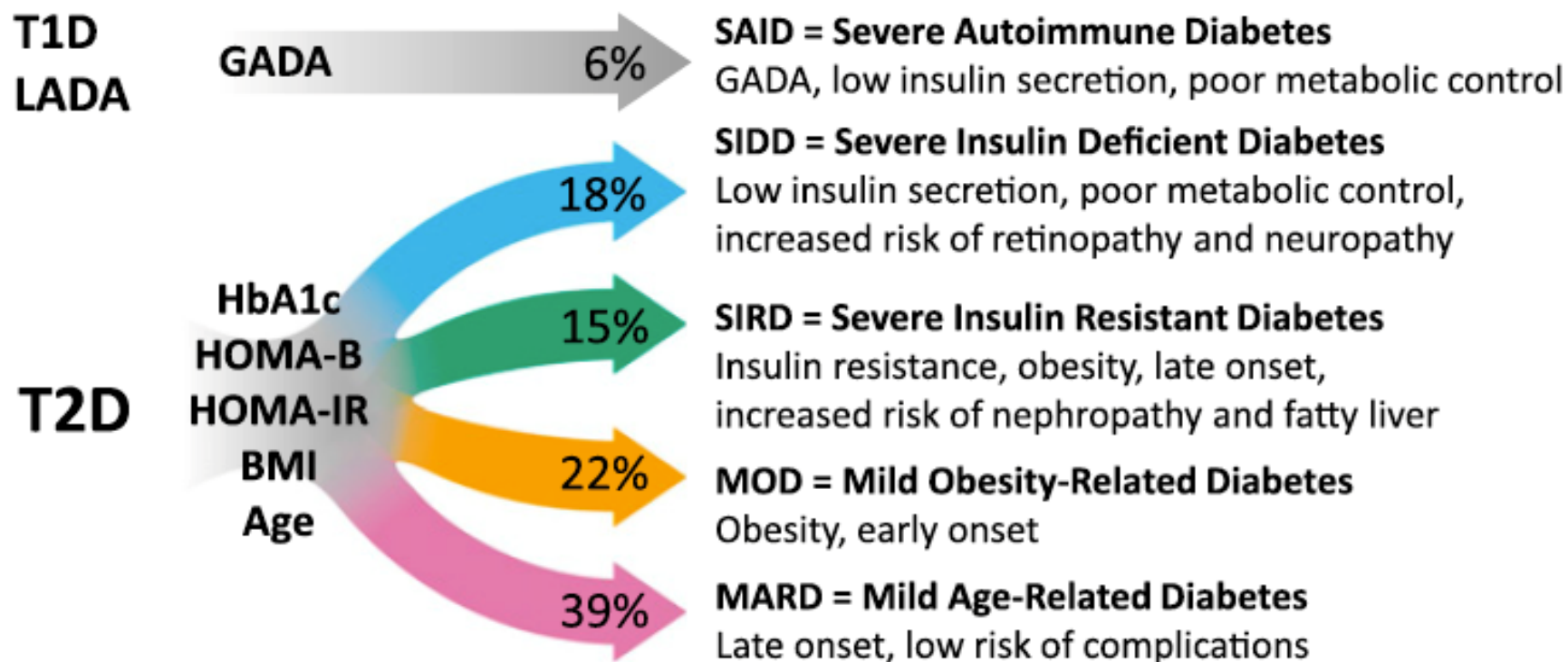
- Anti-GAD antibodies
- Age at diagnosis
- BMI
- A1c
- Beta-cell function (HOMA2-B)\*
- Insulin resistance (HOMA2-IR)\*

\* 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



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



Based on Swedish ANDIS cohort

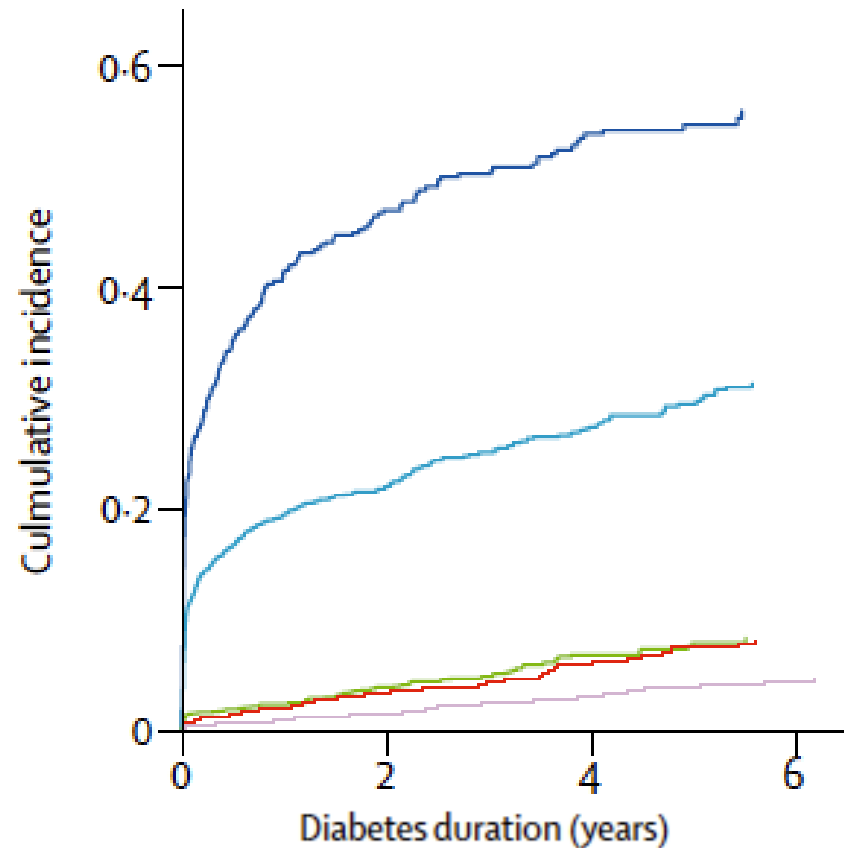
Ahlqvist E et al. Lancet Diab Endocrinol 2018;6:361-69.

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

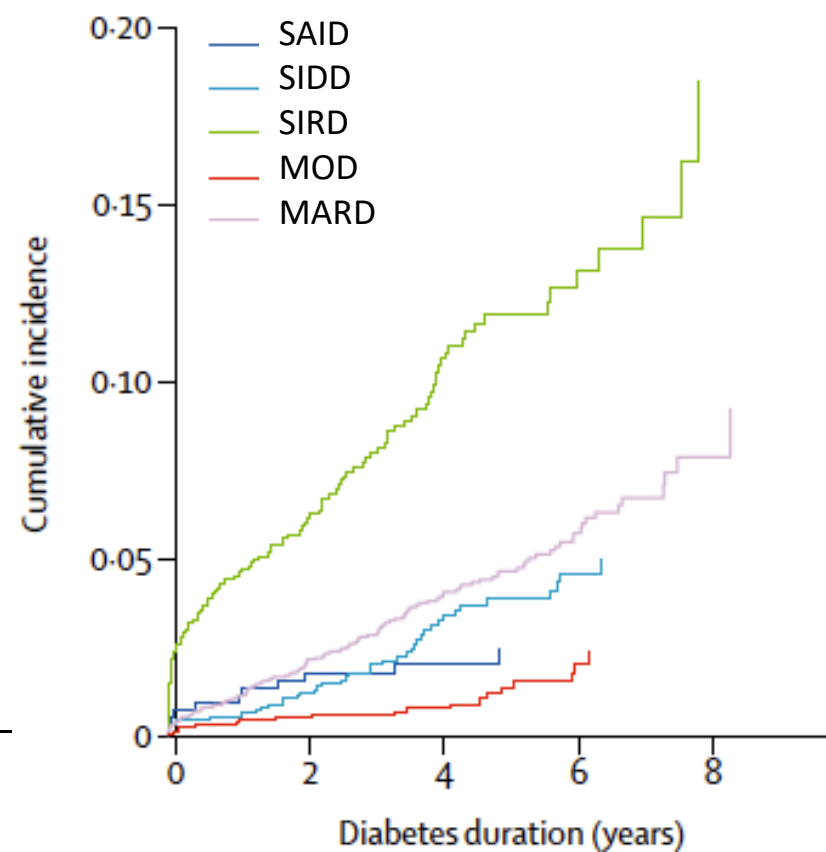


# Diabetes subtype impact treatment and prognosis

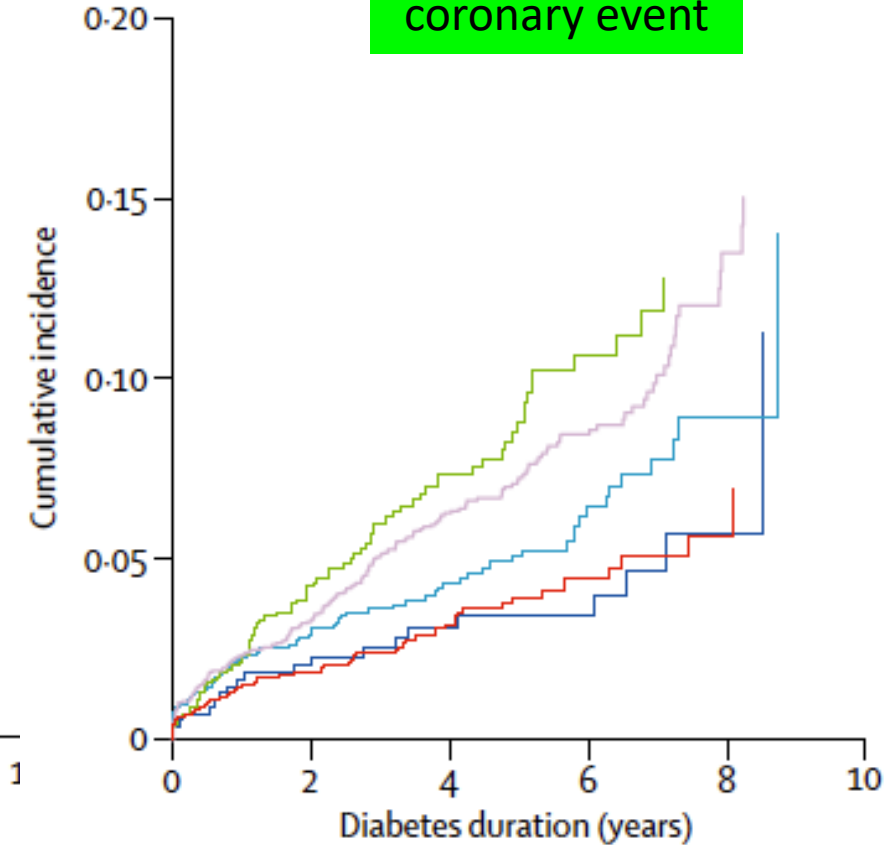
Time to insulin



Time to CKD



Time to coronary event



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/m<sup>2</sup>)

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 (%)

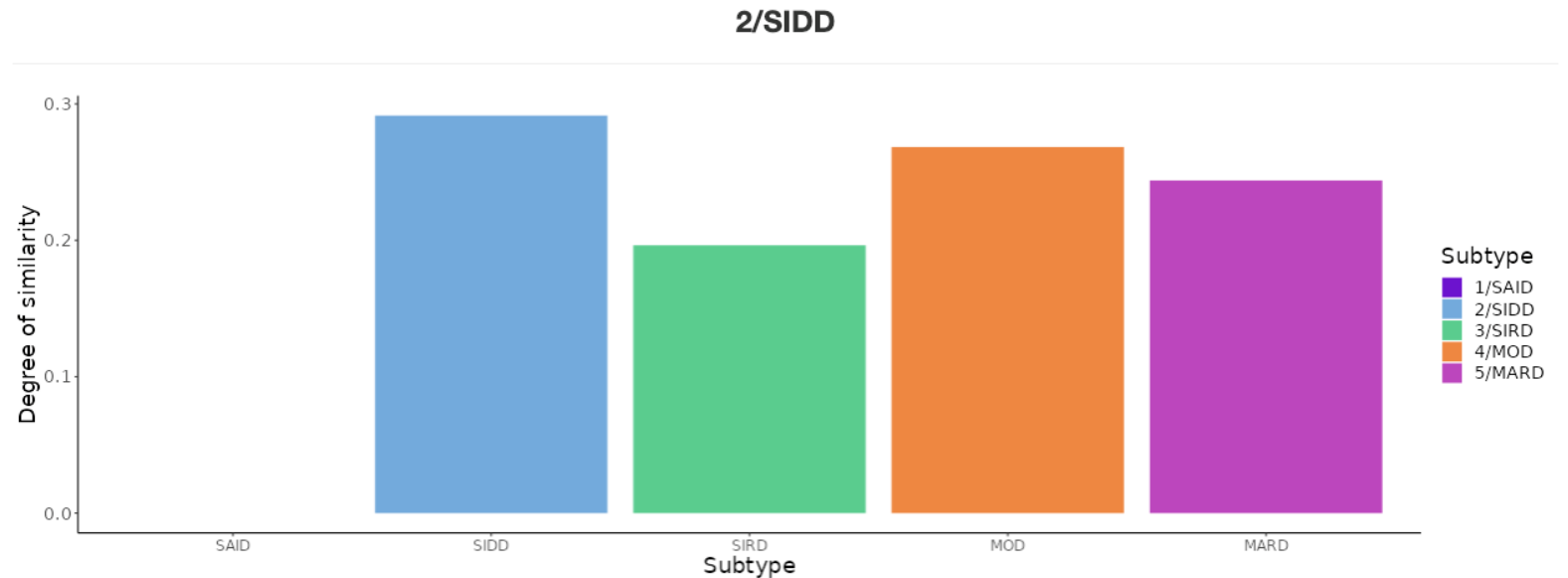
8.5

Sex

Male

Tool [Background information](#)

This person most resembles the diabetes subtype:



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

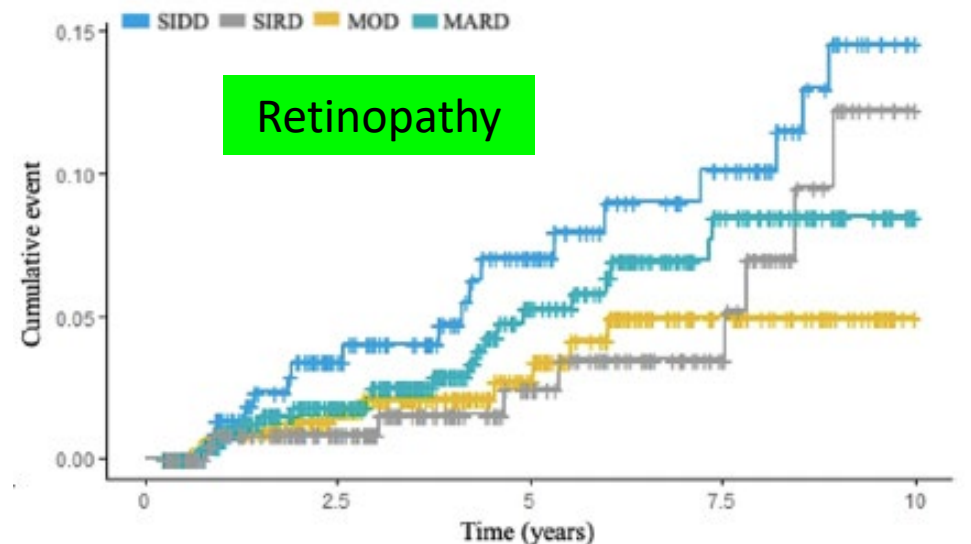
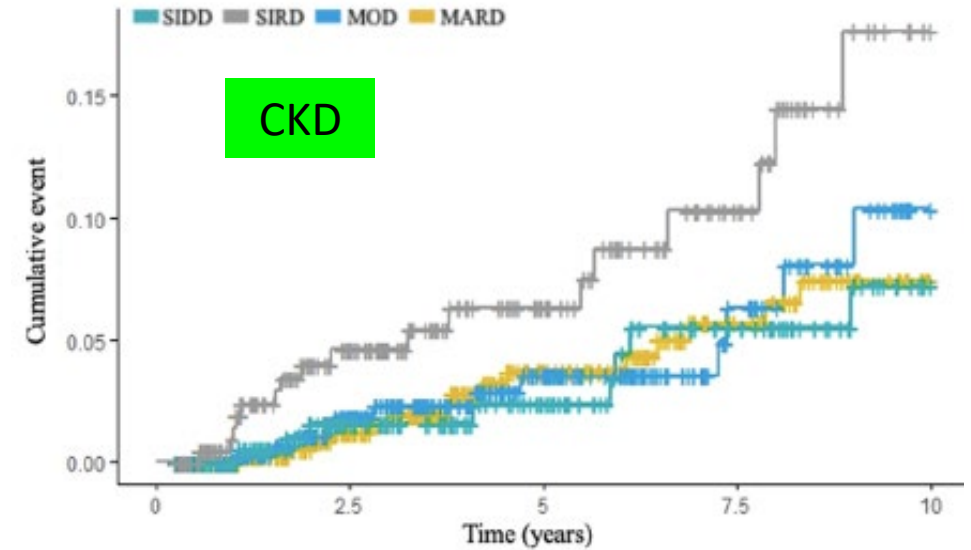
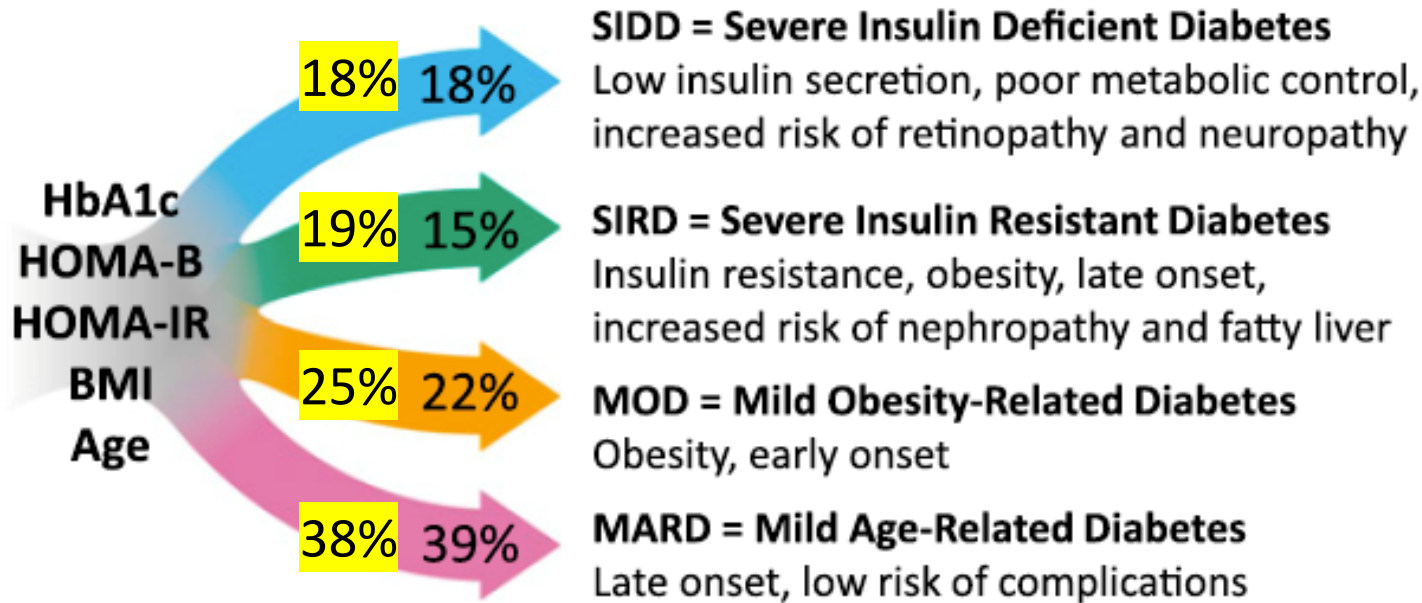
**References**

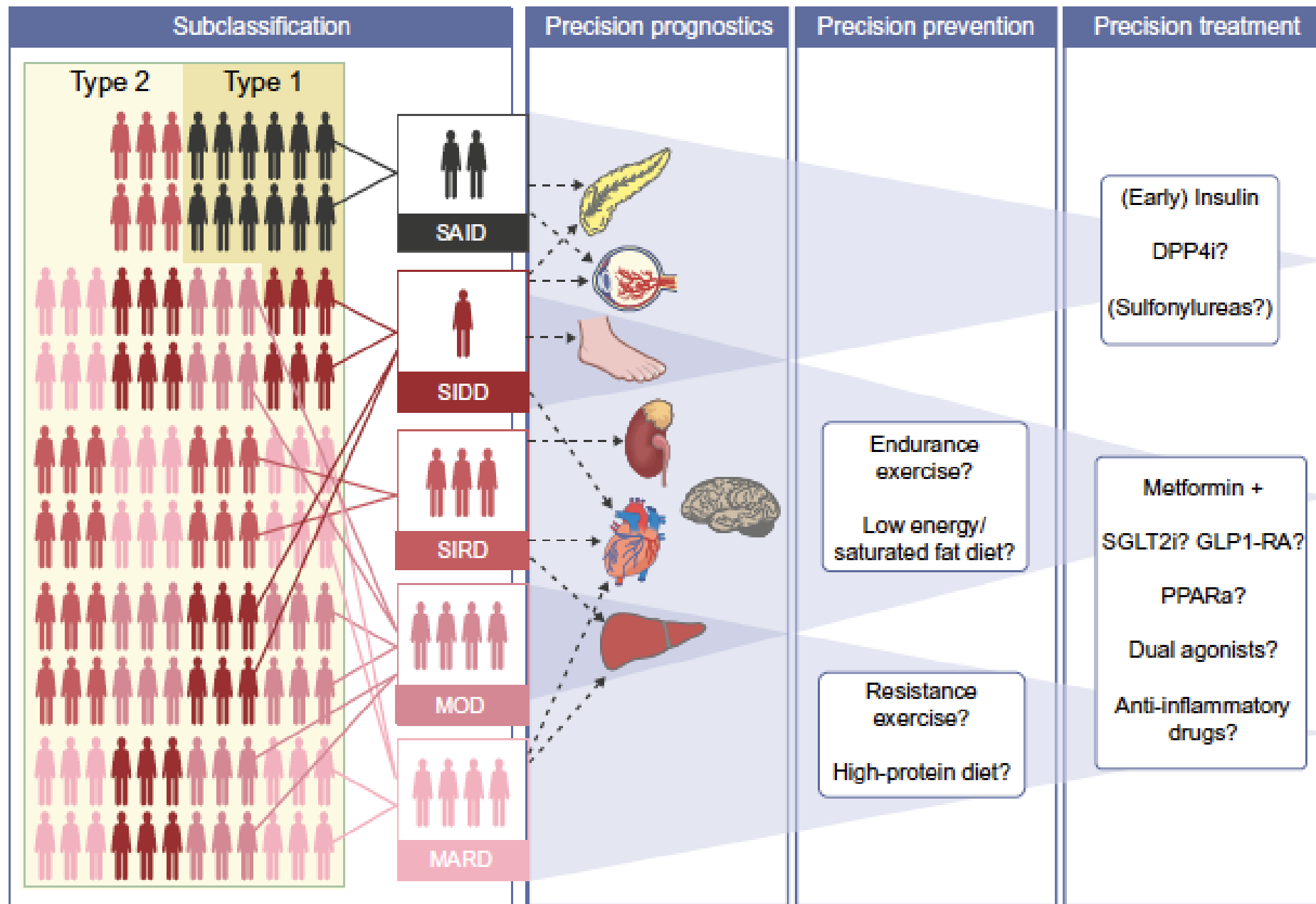
Ahqvist, E., Storm, P., Käräjämäki, A., Martinell, M., Dorkhan, M., Carlsson, A., ... & Groop, L. (2018). Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *The Lancet Diabetes & Endocrinology* 6(5), 361-369.

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







# 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.
<b>Severe insulin-deficient diabetes (SIDD)</b> 	<ul style="list-style-type: none"> <li>Lower age</li> <li>No insulinresistance</li> <li>Normal insulin secretion (C-peptide values &gt; 0.7 nmol/L)</li> <li>Normal adiposity</li> </ul>	<ul style="list-style-type: none"> <li>Middle age</li> <li>No insulinresistance</li> <li>Slightly Low insulin secretion (C-peptide values 0.3–0.7 nmol/L)</li> <li>Normal adiposity</li> </ul>	<ul style="list-style-type: none"> <li>Middle age</li> <li>No insulinresistance</li> <li>Very low insulin secretion (C-peptide values &lt; 0.3 nmol/L)</li> <li>Normal adiposity</li> </ul>	<ul style="list-style-type: none"> <li>Since middle age</li> <li>No insulinresistance</li> <li>Very low insulin secretion (C-peptide values &lt; 0.3 nmol/L)</li> <li>Normal/overweight</li> <li>Increased risk of retinopathy and nephropathy</li> </ul>
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
<b>Severe insulin resistance (SIRD)</b> 	<ul style="list-style-type: none"> <li>Middle age</li> <li>Insulin resistance</li> <li>Hyperinsulinism</li> <li>Visceral adiposity</li> </ul>	<ul style="list-style-type: none"> <li>Middle age</li> <li>Insulin resistance</li> <li>Hyperinsulinism</li> <li>Visceral adiposity</li> </ul>	<ul style="list-style-type: none"> <li>Middle/late age</li> <li>Insulin resistance</li> <li>Hyperinsulinism/partial insulin deficiency</li> <li>Visceral adiposity</li> </ul>	<ul style="list-style-type: none"> <li>Middle/late age</li> <li>Insulin resistance</li> <li>Low insulin secretion</li> <li>Visceral adiposity</li> <li>Increased risk of kidney disease, fatty liver and CVD</li> </ul>
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

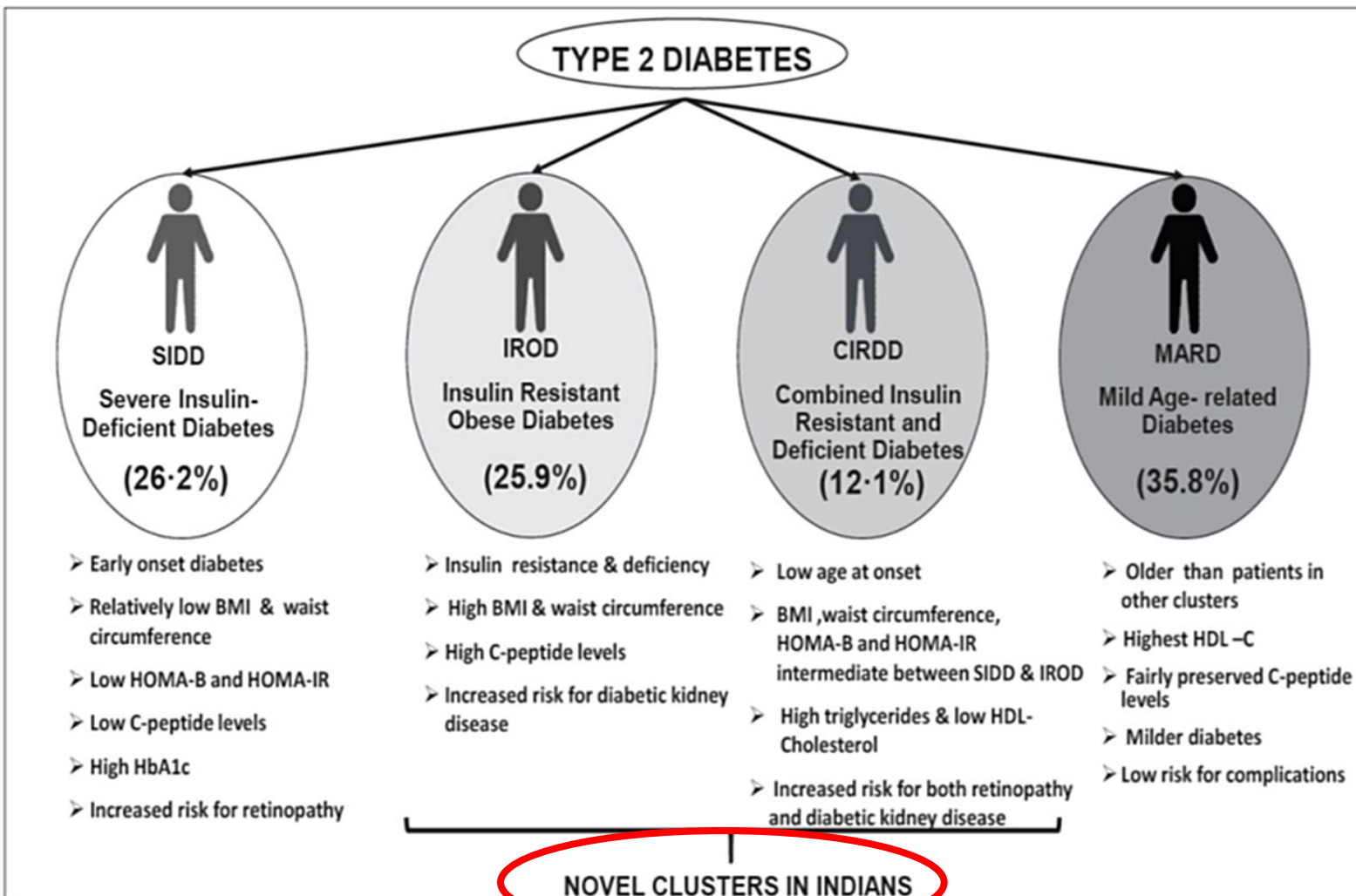


# Diabetes Management Based on the Phenotype and Stage of the Disease: An Expert Proposal from the AGORA Diabetes Collaborative Group

	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.
<b>Mild obesity-related diabetes (MOD)</b> 	<ul style="list-style-type: none"> <li>• Low age</li> <li>• No insulin resistance</li> <li>• Normal insulin secretion</li> <li>• Subcutaneous adiposity</li> </ul>	<ul style="list-style-type: none"> <li>• Middle age</li> <li>• No Insulin resistance</li> <li>• Hyperinsulinism</li> <li>• Subcutaneous adiposity</li> </ul>	<ul style="list-style-type: none"> <li>• Middle age</li> <li>• Insulin resistance</li> <li>• Partial insulin deficiency</li> <li>• Subcutaneous + Visceral adiposity</li> </ul>	<ul style="list-style-type: none"> <li>• Late age</li> <li>• Insulin resistance</li> <li>• Low insulin secretion</li> <li>• Subcutaneous + Visceral adiposity</li> <li>• <b>Mechanical complications</b></li> </ul>
<i>Follow-up</i>	Annually		2–3/Year	
<i>Recommended management</i>	LSM /Bx Surgery DMDs		LSM DMDs + metf/pio	LSM DMDs + metf/pio + basal insulin
<i>Treatment goals</i>	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%	<b>HbA1c &lt; 8% LDL-c, BP, weight: Individualize</b>
<b>Mild age-related diabetes (MARD)</b> 	<ul style="list-style-type: none"> <li>• Late onset/elderly</li> <li>• No insulinresistance</li> <li>• Normal insulin secretion</li> <li>• Normal adiposity</li> </ul>	<ul style="list-style-type: none"> <li>• Late onset/elderly</li> <li>• No insulinresistance</li> <li>• Slightly Low insulin secretion (C-peptide values 0.3–0.7 nmol/L)</li> <li>• Normal adiposity</li> </ul>	<ul style="list-style-type: none"> <li>• Late onset/elderly</li> <li>• No insulinresistance</li> <li>• Low insulin secretion</li> <li>• Normal adiposity/sarcopenia</li> </ul>	<ul style="list-style-type: none"> <li>• Late onset/elderly</li> <li>• No insulinresistance</li> <li>• Low insulin secretion</li> <li>• Underweight risk /sarcopenia</li> <li>• <b>Low risk of complications</b></li> </ul>
<i>Follow-up</i>	Annually		2/Year	
<i>Recommended management</i>	NA		Nutritional support Safer antidiabetic drugs	Nutritional support Safer antidiabetic drugs + basal insulin
<i>Treatment goals</i>	HbA1c < 7% LDL-c, BP, weight: Individualize	HbA1c < 7% LDL-c, BP, weight: Individualize	HbA1c < 7.5% LDL-c, BP, weight: Individualize	<b>HbA1c &lt; 8% LDL-c, BP, weight: Individualize</b>

\*Or Upper limit of normality for HbA1c

# 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



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



typic variables. Attempts<sup>20</sup> 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 (SIDDD) (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<sup>21</sup> to suggest that these “clusters” differ in the natural history of the disease, risk of complications, and response to treatment.

# 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<sup>1\*†</sup>, Tatsuya Kondo<sup>2†</sup>, Yasuharu Ohta<sup>3†</sup>, Atsushi Goto<sup>4</sup>, Daisuke Tanaka<sup>5</sup>, Hiroaki Satoh<sup>6</sup>, Daisuke Yabe<sup>7</sup>, Rimei Nishimura<sup>8</sup>, Norio Harada<sup>5†</sup>, Hideki Kamiya<sup>9†</sup>, Ryo Suzuki<sup>10†</sup>, Toshimasa Yamauchi<sup>11†</sup>, JDS Committee on Consensus Statement Development

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

Determine if the patient has a relative/absolute indication for insulin

No

Yes

Insulin therapy

Determine the patient's HbA1c target value

In reference to the "Kumamoto Declaration 2013" and "Glycemic targets (HbA1c values) for older people with diabetes"

Step 1

Select medications to address the diabetes pathology involved

Non-obese patient

[likely involving insulin insufficiency]

DPP-4 inhibitors, biguanides,  $\alpha$ -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,  $\alpha$ -glucosidase inhibitors, imeglimin, and tirzepatide

While insulin resistance is analyzed 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  $\geq 25$  kg/m<sup>2</sup>  
■ Abdominal standard representing visceral fat accumulation in Japan: men:  $\geq 85$  cm, women:  $\geq 90$  cm

Step 2

Giving due consideration to ensuring safety

Avoid options marked "red" for areas of interest listed in the separate table, where caution should be exercised in the use thereof.

Rule of thumb 1: Avoid SUs and glinides in older people at high risk of hypoglycemia

Rule of thumb 2: Avoid biguanides, SUs, thiazolidinediones, and glinides for renal excretion in people with renal impairment (Severe renal impairment is a contraindication for SUs, biguanides, and thiazolidinediones)

Rule of thumb 3: Avoid thiazolidinediones and biguanides in people with heart failure (in whom they are contraindicated)

Step 3

Weighing the additional medication benefits for comorbidities

Chronic kidney disease (CKD)\*

Heart Failure (HF)

Cardiovascular disease (CVD)

SGLT2 inhibitor†, GLP-1 receptor agonist

SGLT2 inhibitor†

SGLT2 inhibitor, GLP-1 receptor agonist

\*: especially overt nephropathy

†: some medications

Step 4

Select medication options with relevant patient characteristics in mind

in reference to adherence rates and medication costs listed in the separate table

Review the current medication regimen for possible revision every 3 months

Determine if the patient has a relative/absolute indication for insulin

No

Yes

Insulin therapy

Determine the patient's HbA1c target value

In reference to the "Kumamoto Declaration 2013" and "Glycemic targets (HbA1c values) for older people with diabetes"

## Step 1

# Select medications to address the diabetes pathology involved

## Non-obese patient

[likely involving insulin insufficiency]

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\*: To improve postprandial hyperglycemia; <sup>†</sup> 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]

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\*: especially over: nephropathy  
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## Step 4

Select medication options with relevant patient characteristics in mind

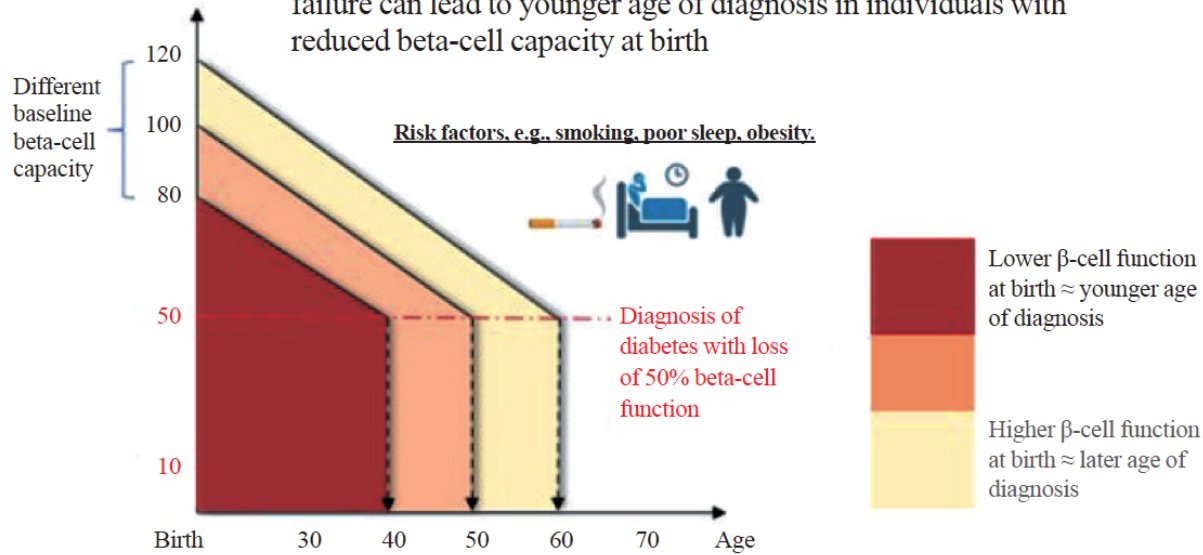
in reference to adherence rates and medication costs listed in the separate table

Review the current medication regimen for possible revision every 3 months



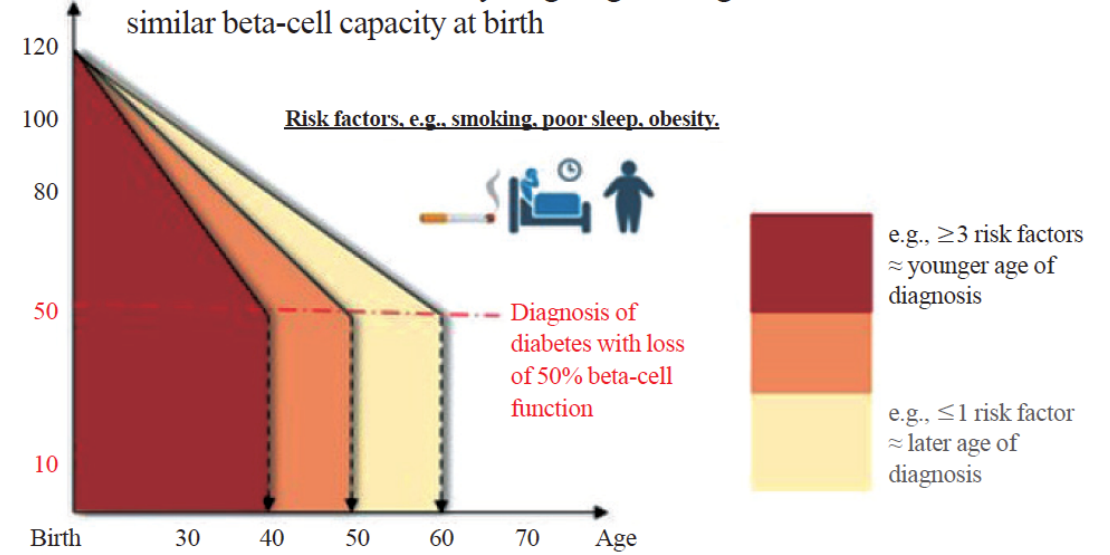
## A. Different beta-cell capacity at birth

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

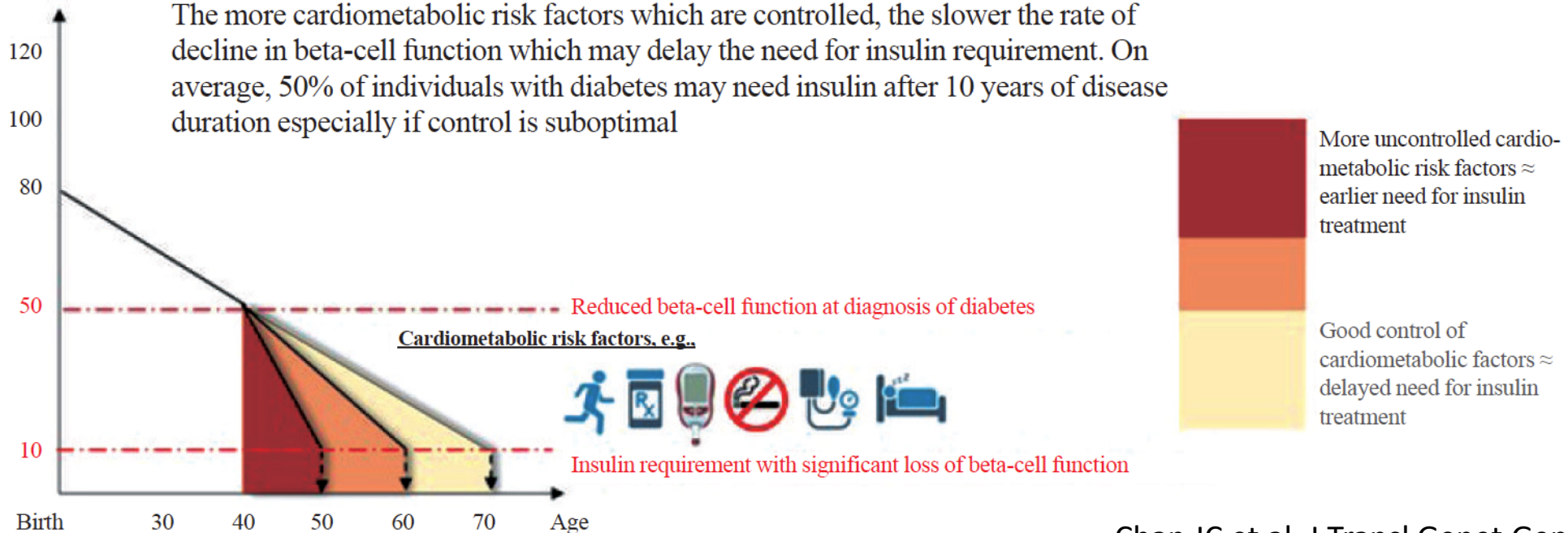


## B. Similar beta-cell capacity at birth

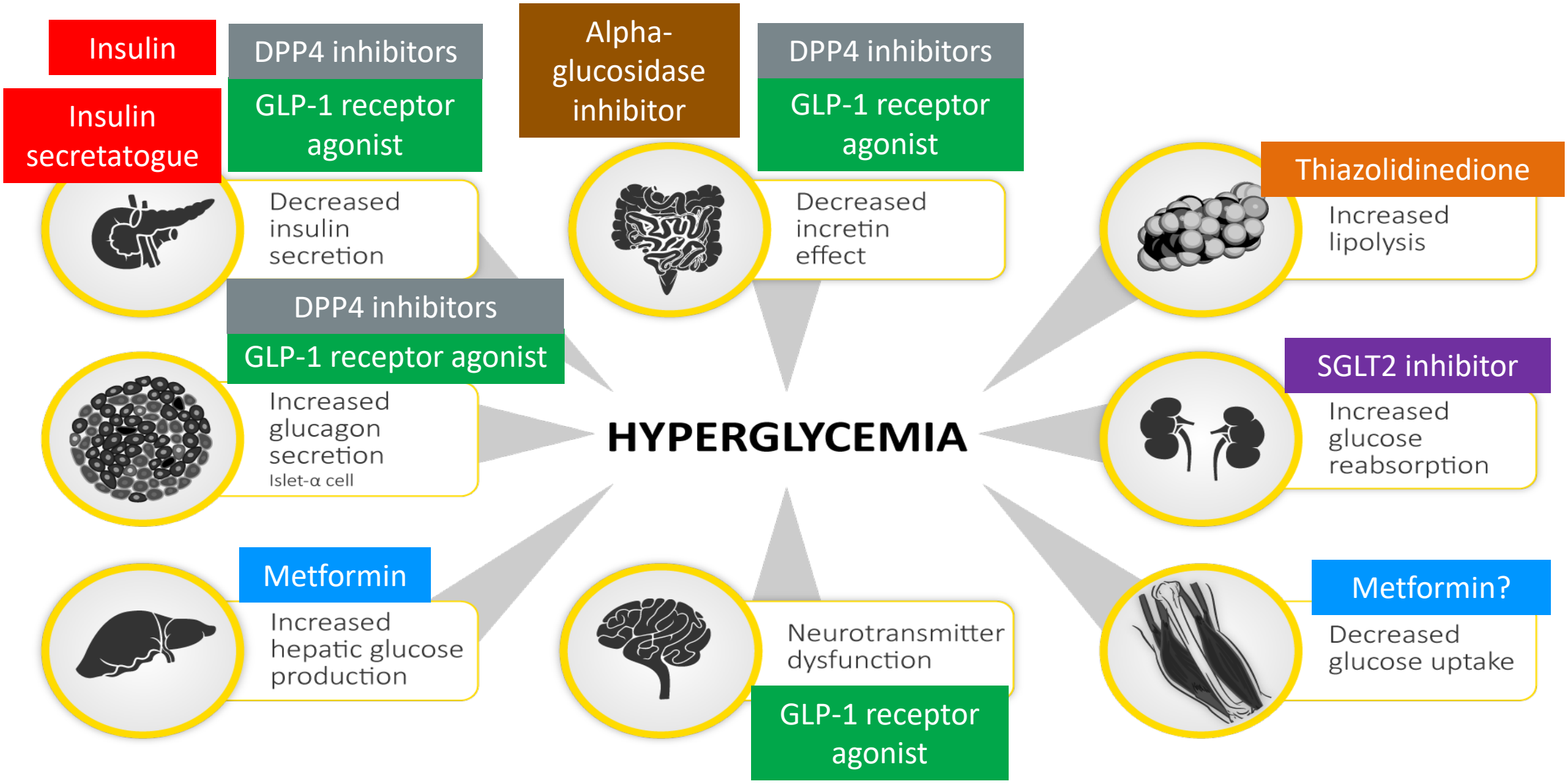
Increasing numbers of acquired risk factors can accelerate trajectory of beta-cell failure and lead to younger age of diagnosis in individuals with similar beta-cell capacity at birth



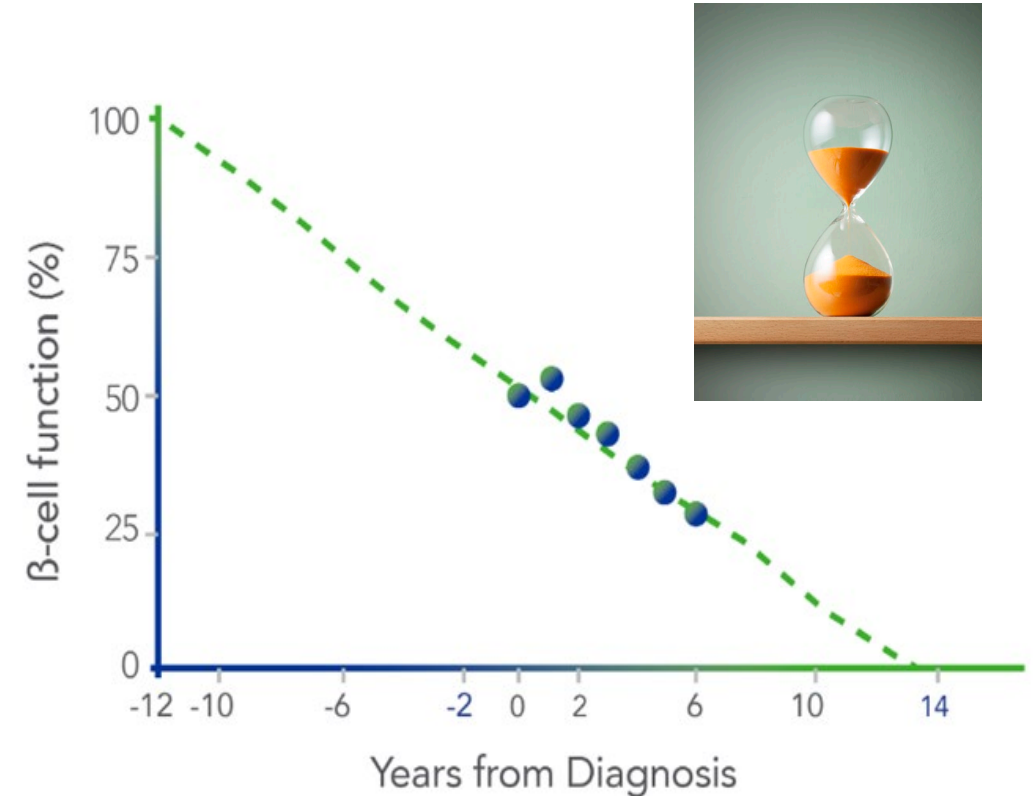
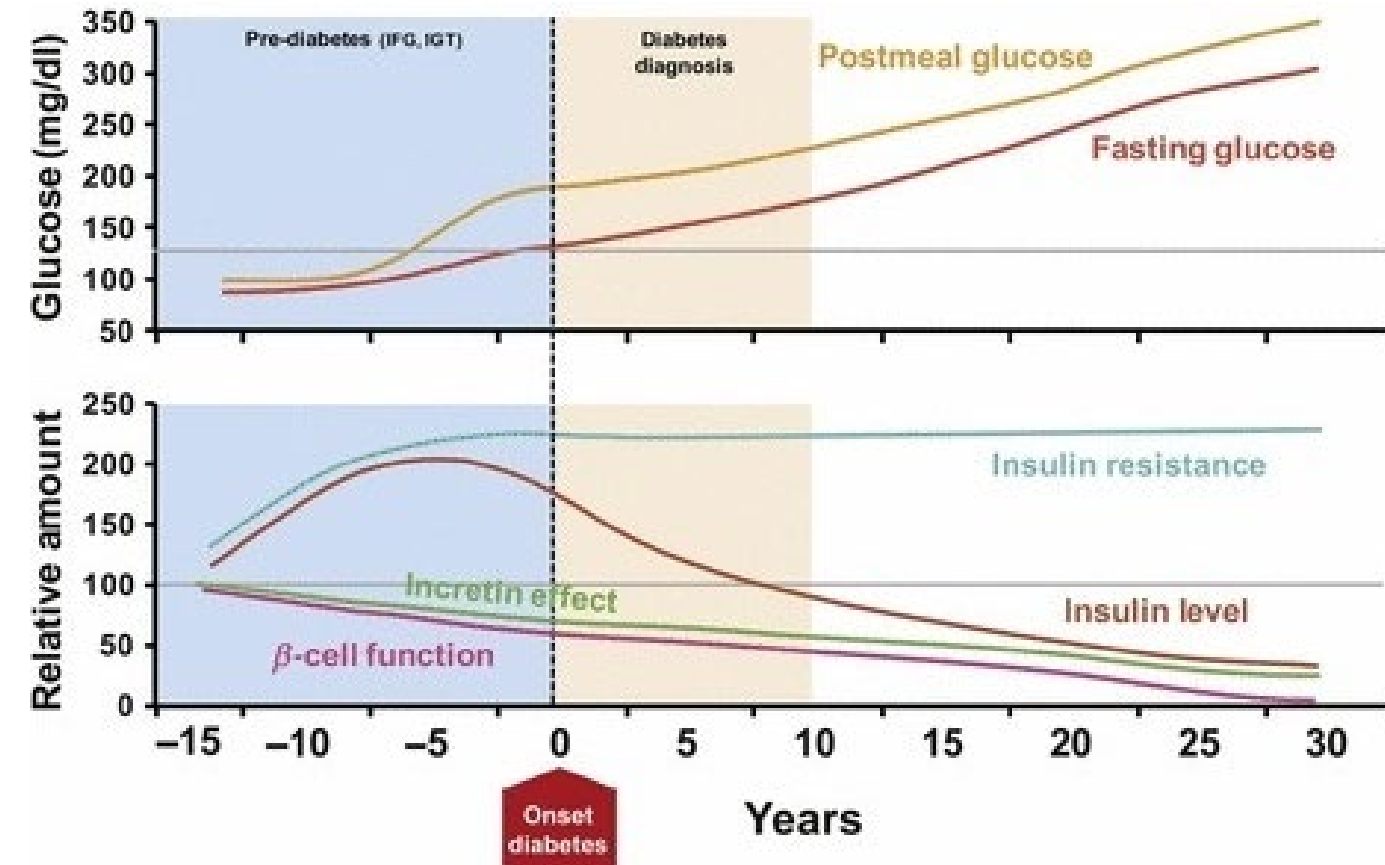
The more cardiometabolic risk factors which are controlled, the slower the rate of decline in beta-cell function which may delay the need for insulin requirement. On average, 50% of individuals with diabetes may need insulin after 10 years of disease duration especially if control is suboptimal



# HYPERGLYCEMIA



# Natural history of type 2 diabetes



# Menin Inhibition and Beta-Cell Biology

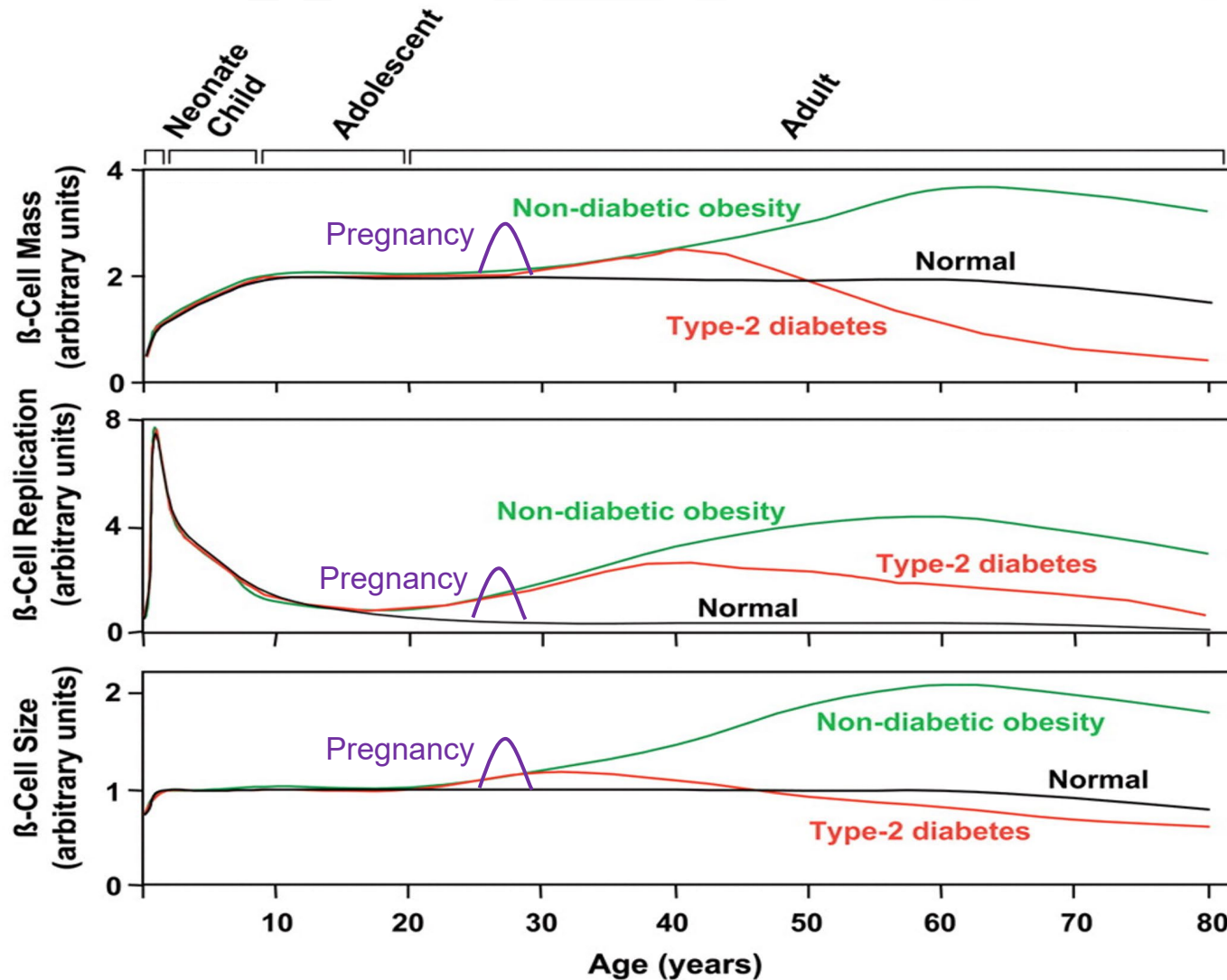
Rohit N. Kulkarni, MD, PhD  
Joslin Diabetes Center



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# Beta Cell Compensation in Physiological and Pathophysiological States in Mammals



## Normal Beta Cell Biology

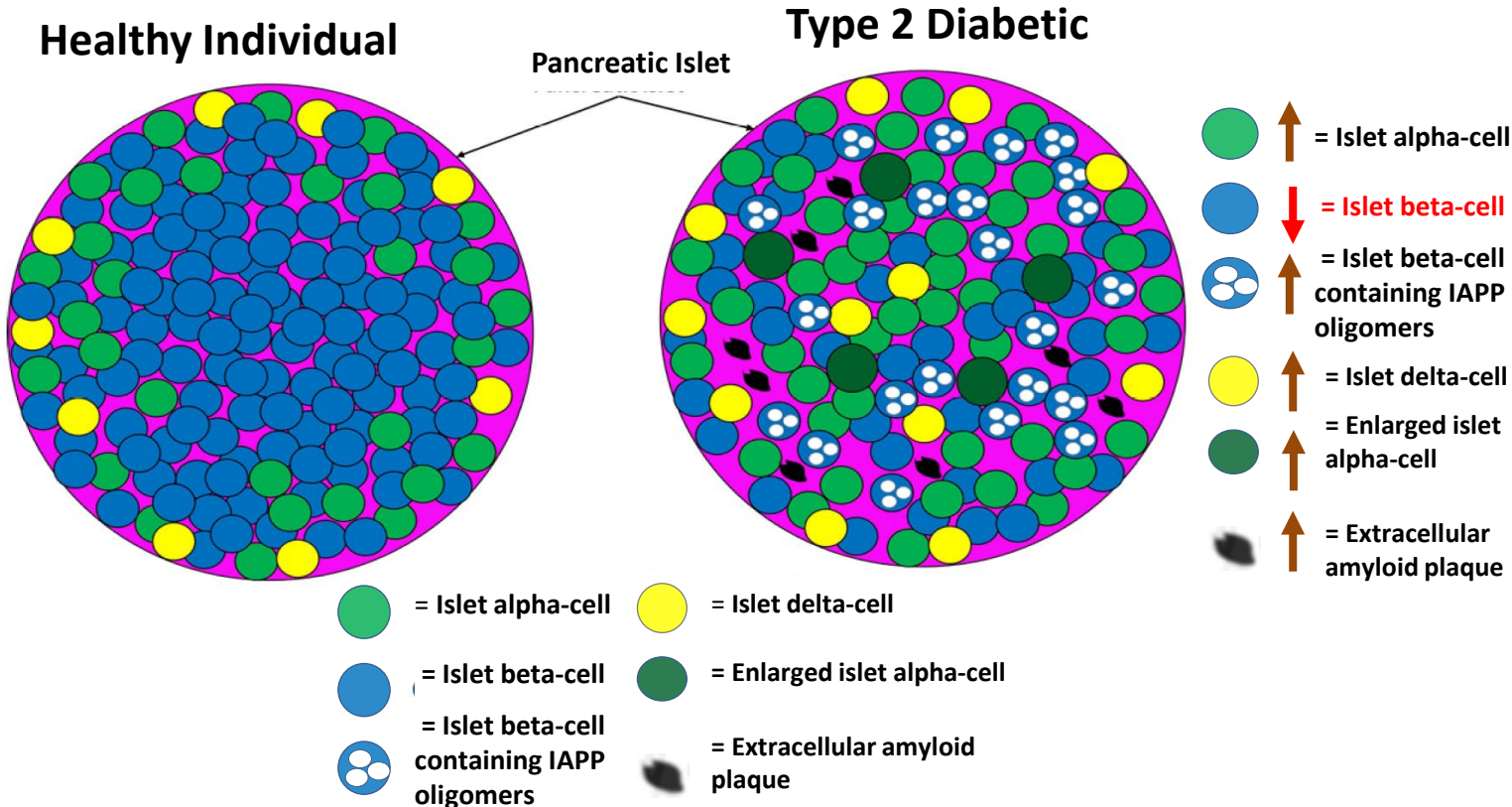
- 97% of the human beta cell pool is established by age 20
- Beta cell lifespan in humans is >20-30 yrs
- Many (but not all) beta cells remain postmitotic for their lifetime

$\beta$ -Cell Mass

$\beta$ -Cell Replication

$\beta$ -Cell Size

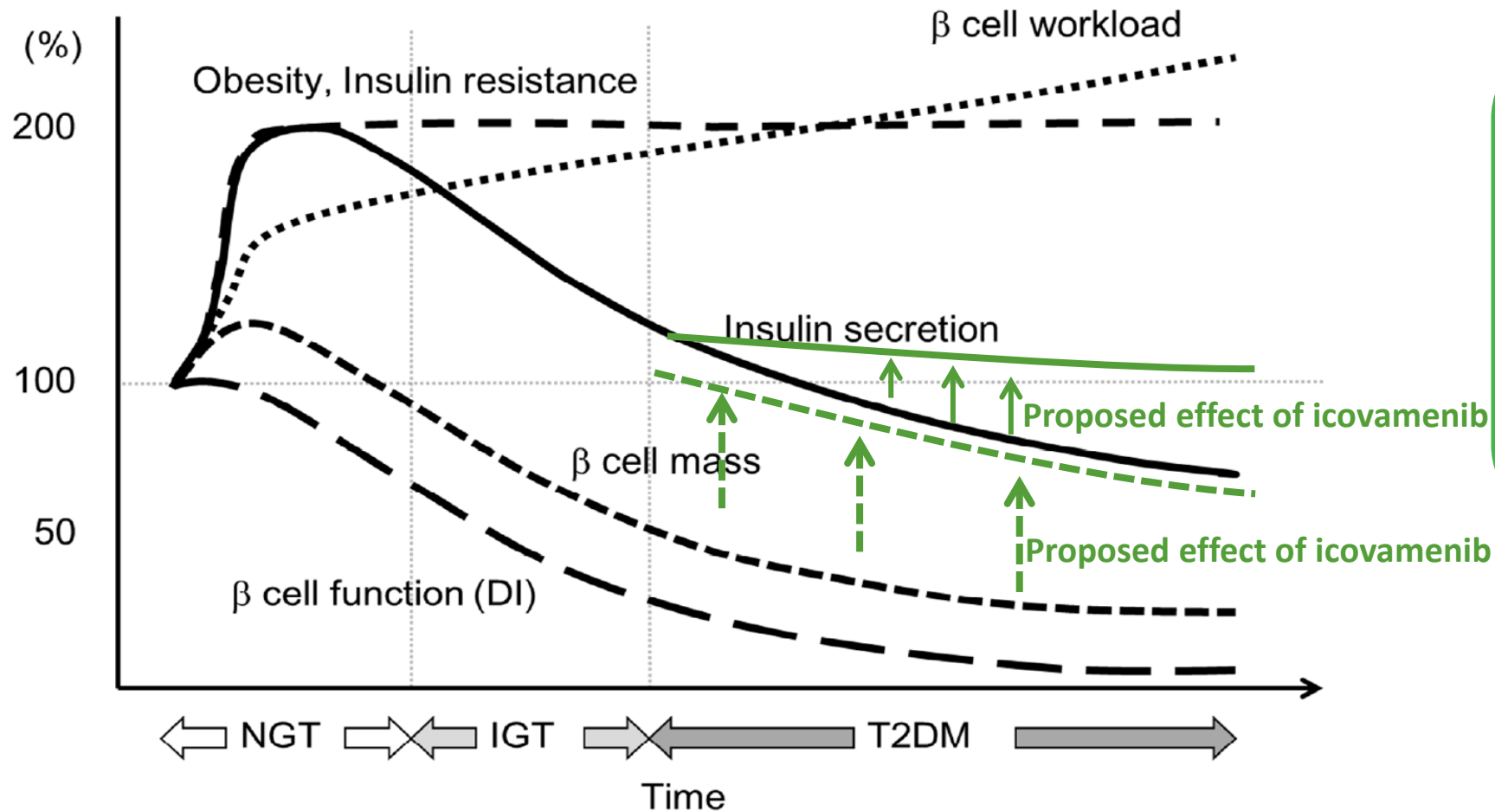
# Type 1 and 2 Diabetes Progression Results in Ongoing Beta Cell Loss



- Beta cell mass is decreased by  $\geq 50\%$  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

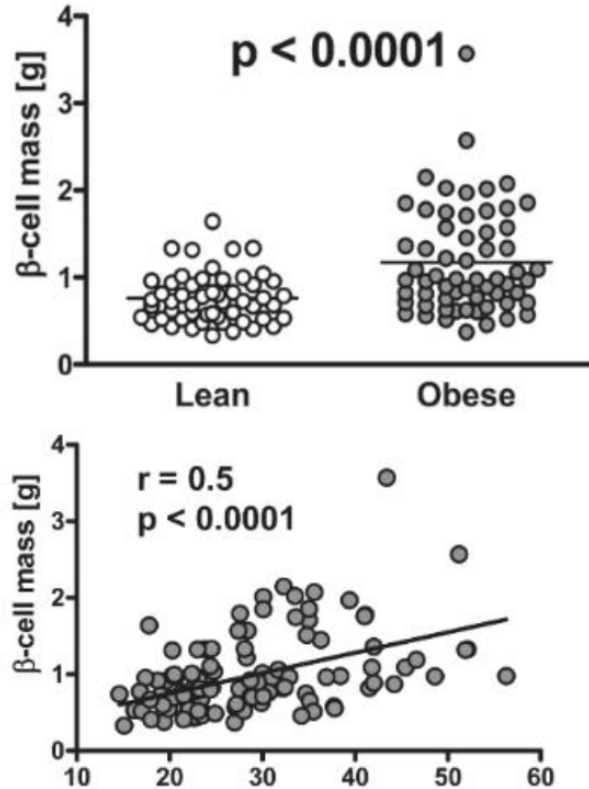
\*Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744`

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



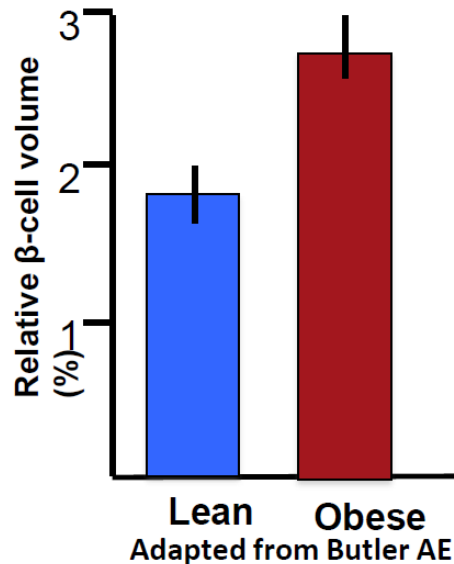
Biomea's covalent menin inhibitor, icovamenib, is designed to increase the beta cell mass and function, increasing insulin production to achieve glycemic control - without the need for continuous medication

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

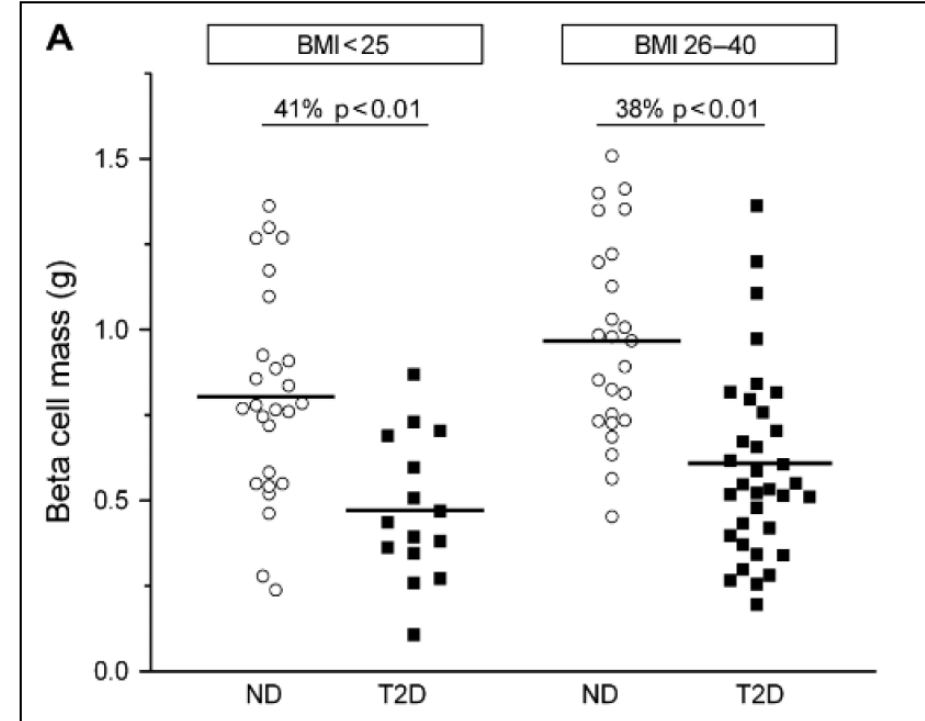


Saisho Y et al, *Diabetes care*, August 2012

$\beta$ -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

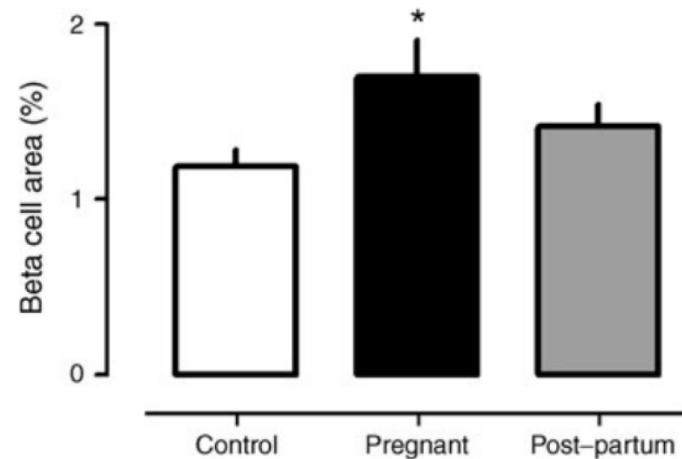
**TABLE II**  
*The endocrine pancreas in non-pregnant and pregnant women*

	Endocrine tissue (per cent)	$\beta$ cells (per cent)
<i>Non-pregnant women</i>		
1	1.6	75
2	1.5	68
3	2.0	78
4	1.4	69
5	1.3	74
<b>Mean <math>\pm</math> SD</b>	<b>1.56 <math>\pm</math> 0.27</b>	<b>72.8 <math>\pm</math> 4.2</b>
<i>Pregnant women</i>		
1	3.2	81
2	3.1	83
3	2.9	79
4	3.6	84
5	3.7	83
<b>Mean <math>\pm</math> SD</b>	<b>3.3 <math>\pm</math> 0.3</b>	<b>82.0 <math>\pm</math> 1.8</b>
<b>P</b>	<b>&lt;0.001</b>	<b>&lt;0.005</b>

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

"This quantitative morphological study shows a **marked enlargement of the islets of Langerhans in pregnant women.**"

F. A. Van Assche et al. *British Journal of Obstetrics and Gynaecology*, 1978 November



Butler et al. *Diabetologia*. 2010

"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."

Hughes et al. *Endocrinology*, March 2011, 152(3):847-855

## 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  $\beta$  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; Saudak *et al.*, 1975). In the pregnant rat it has been shown that the number of insulin producing  $\beta$  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  $\mu$ m 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).

## Participation of Akt, Menin, and p21 in Pregnancy-Induced $\beta$ -Cell Proliferation

Elizabeth Hughes and Carol Huang

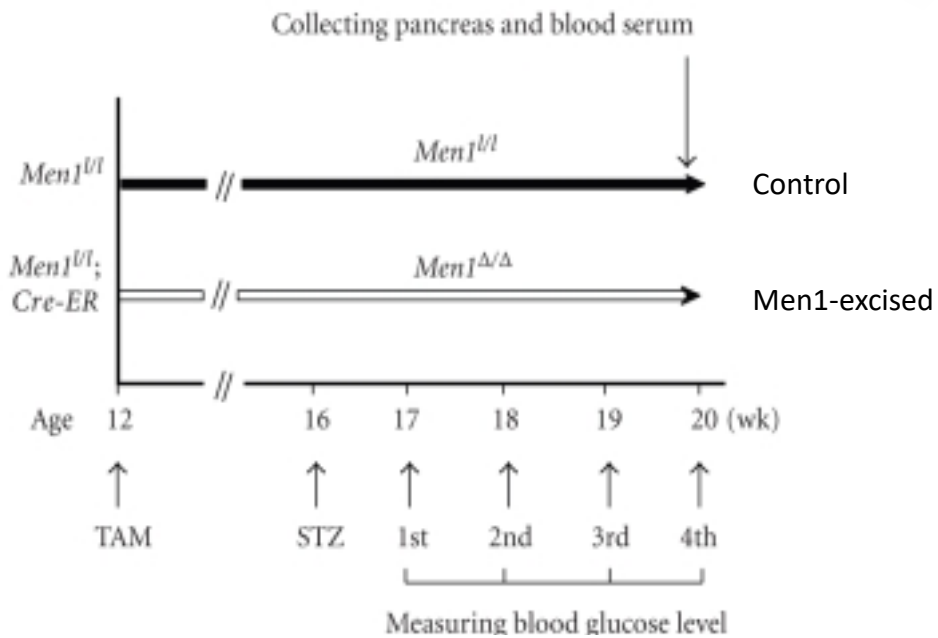
University of Calgary, Faculty of Medicine, Departments of Pediatrics and Biochemistry and Molecular Biology, Calgary, Alberta, Canada T2N 4N1

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

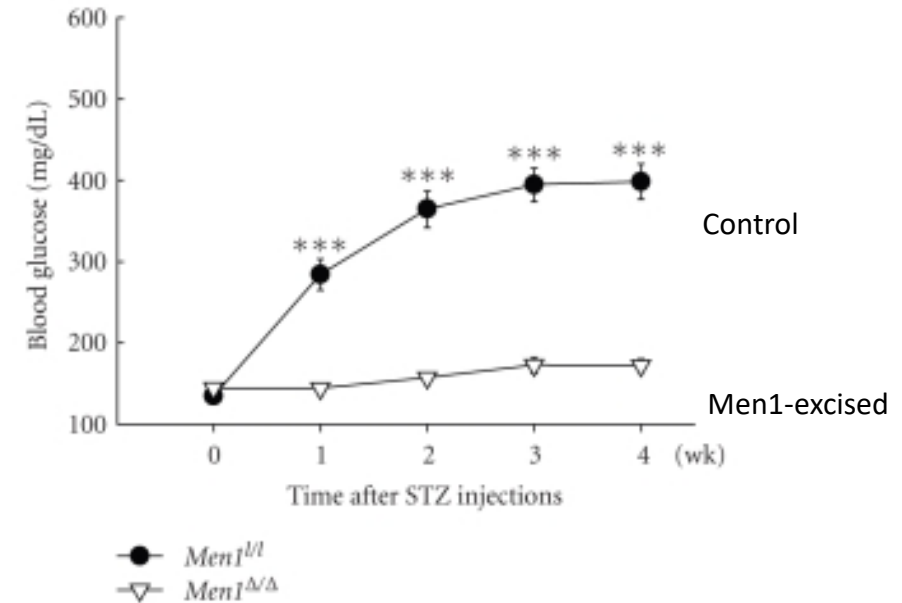


# Potential for Menin Inhibition Demonstrated by Beta Cell Ablation Diabetes Model in MEN1-Excised Mice

## MEN1 Excision Prevents Development of STZ-induced Hyperglycemia

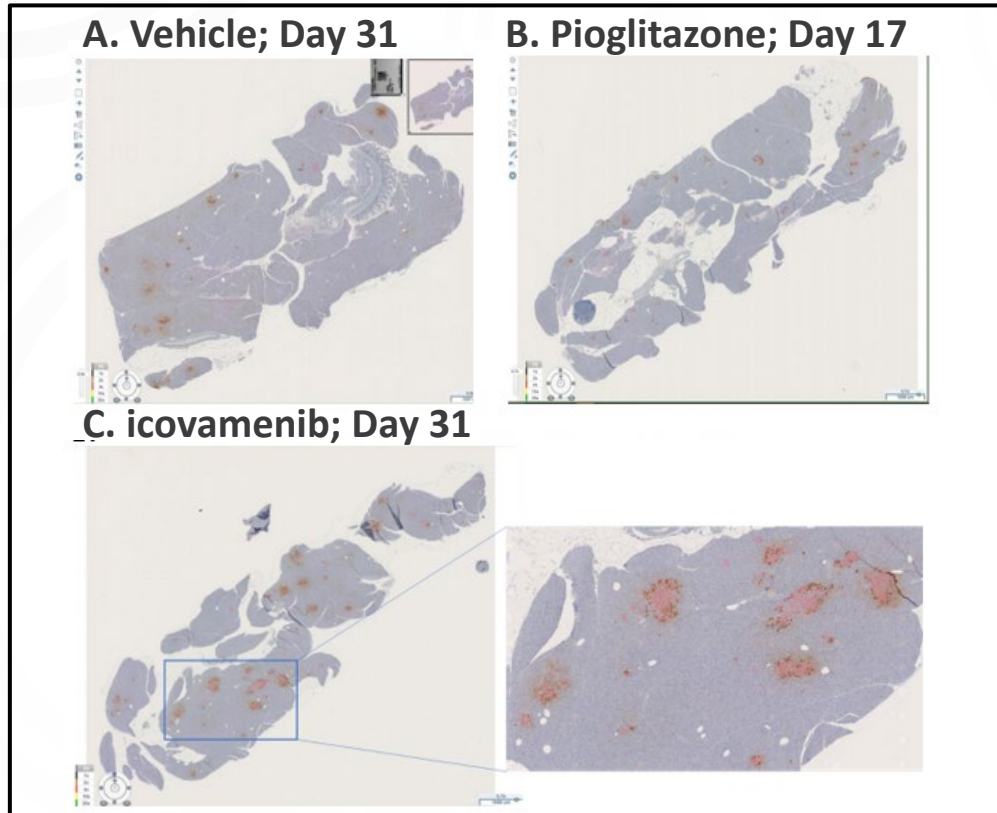


Multiple low-dose streptozotocin (MLD-STZ) administered to the control and *Men1*-excised mice to induce beta cell damage and a diabetes-like environment

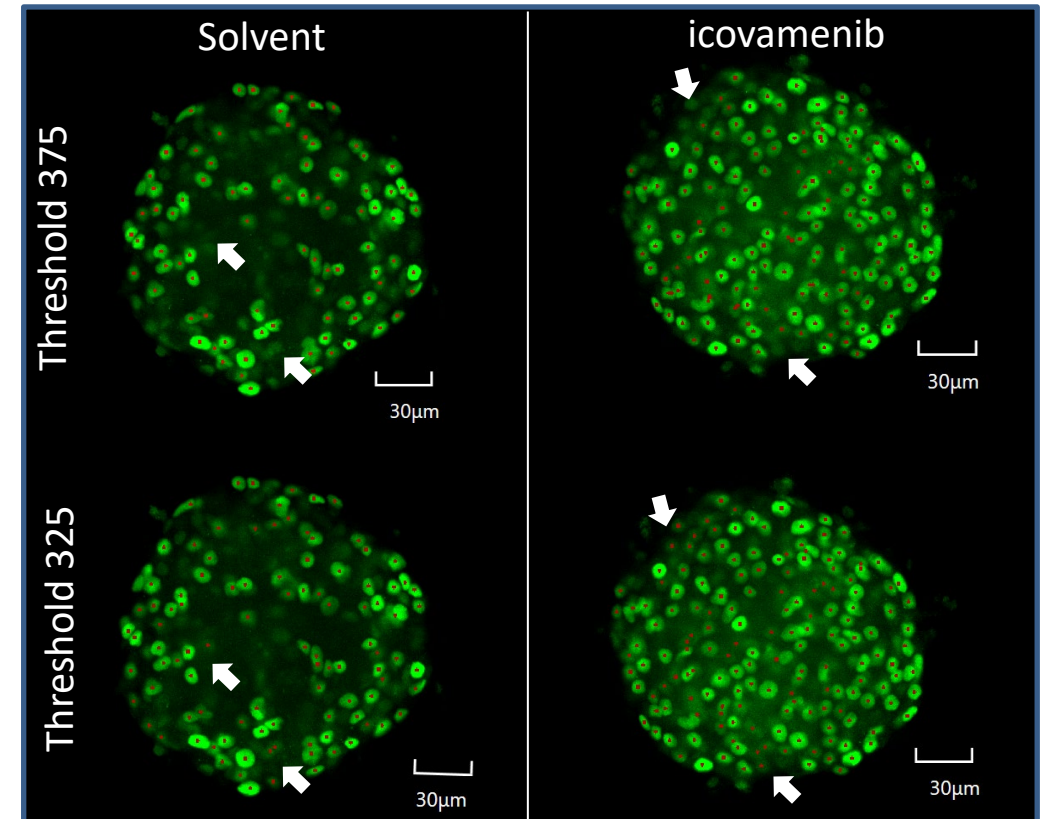


*Men1*-excised mice did not develop hyperglycemia in STZ model, which was observed in the control group

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



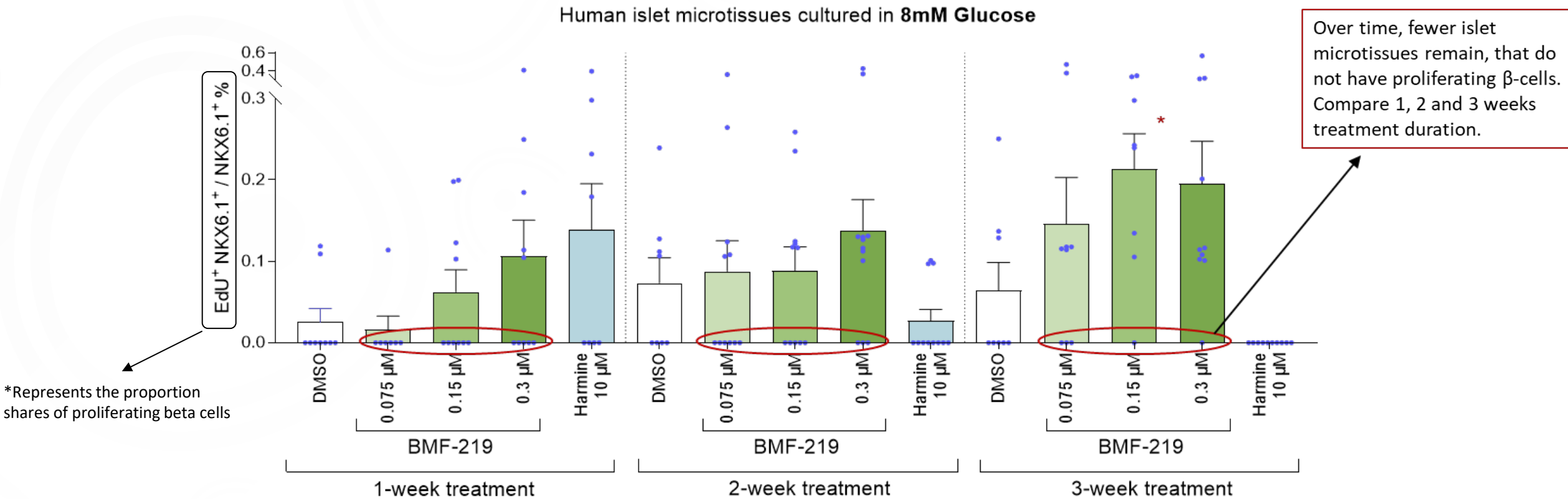
**ZDF Diabetic Model:** A) Vehicle-treated animal, Day 31. Beta islets display low congregation and growth, while alpha cells dominate. B) Pioglitazone-treated animal, Day 17. Beta islets display congregation and growth. C) Icovamenib treated animal, Day 31. Beta islets display high congregation and 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



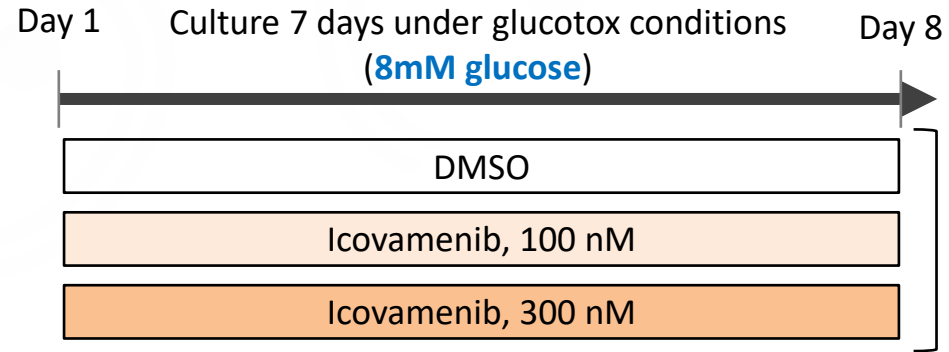
Data represent mean  $\pm$ SEM of 1 donor with n = 9-12 technical replicates.  
 One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001

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

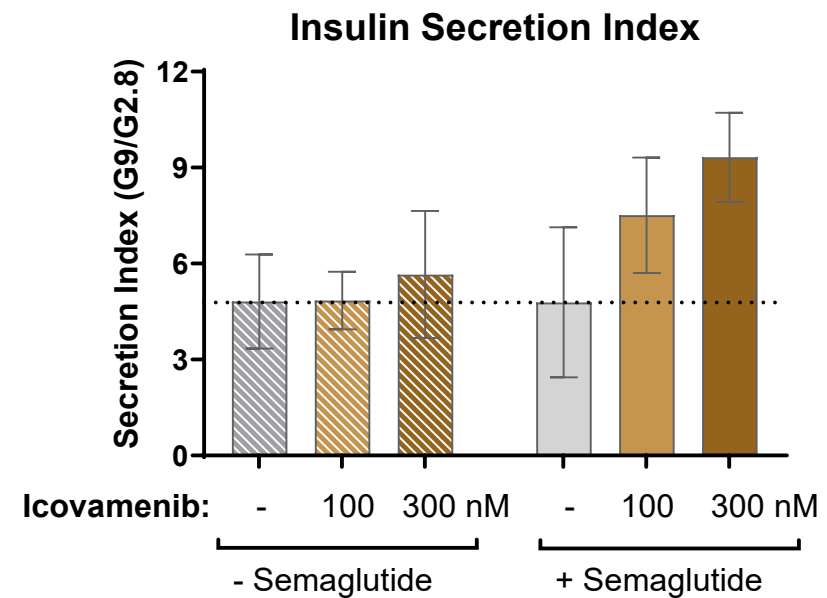
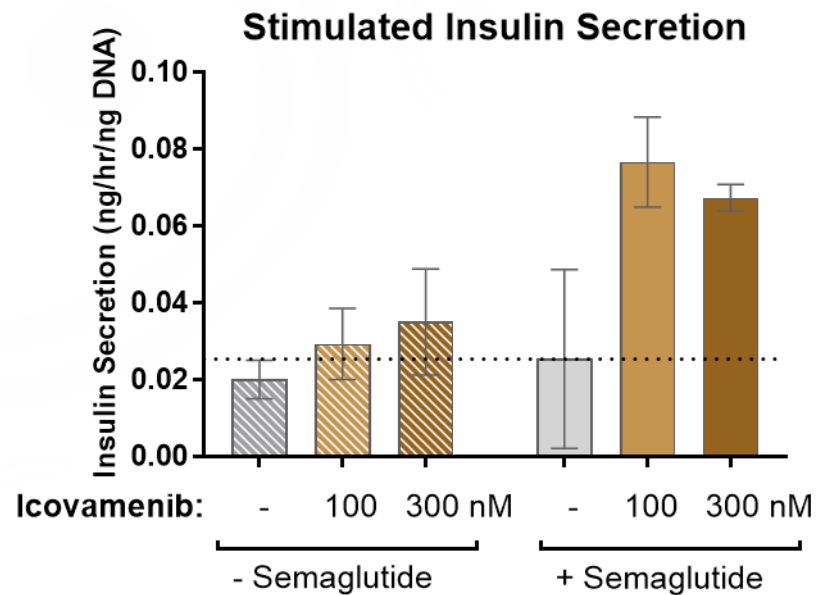
Cadaver derived  
human islets



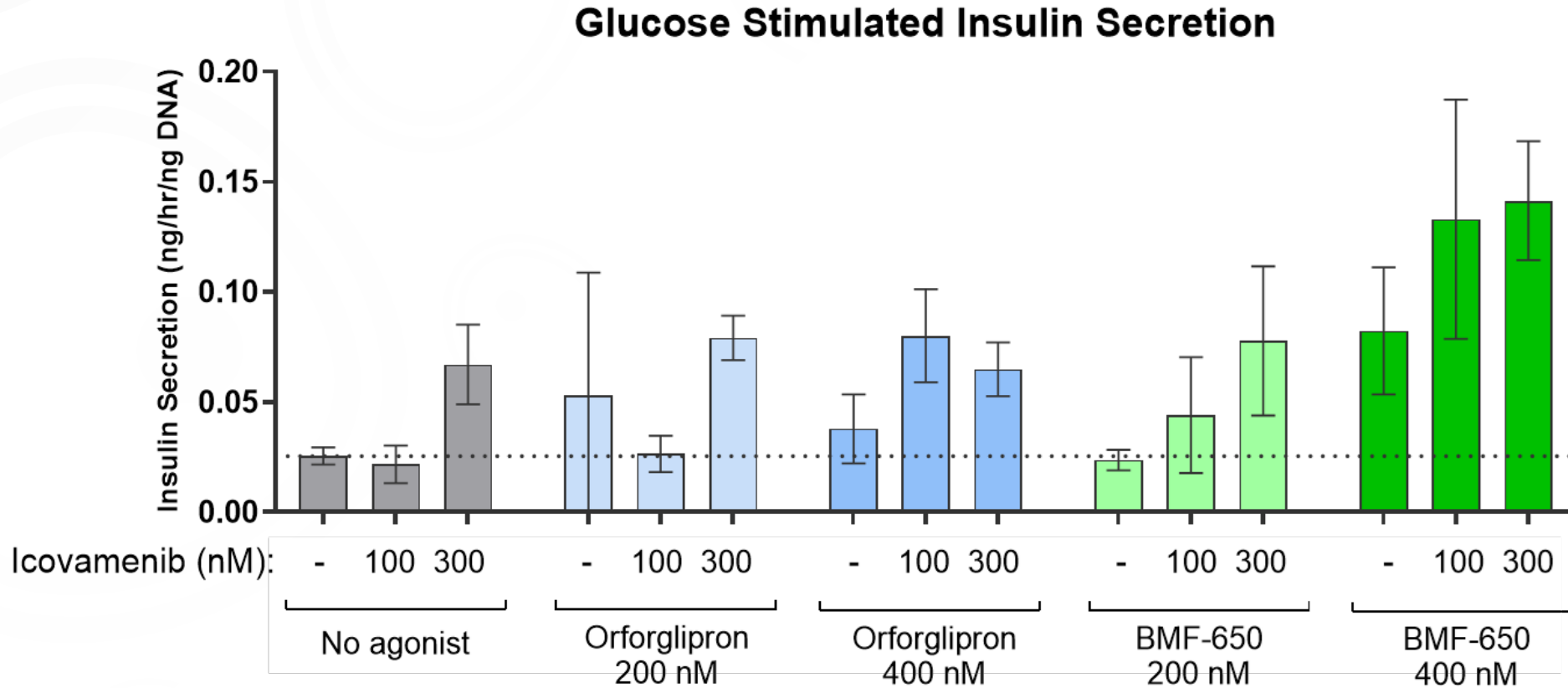
Non-diabetic donor:  
41yr Hispanic male, BMI 27.8, HbA1c 5.3%



Perform GSIS +/- **Semaglutide**  
(200nM)

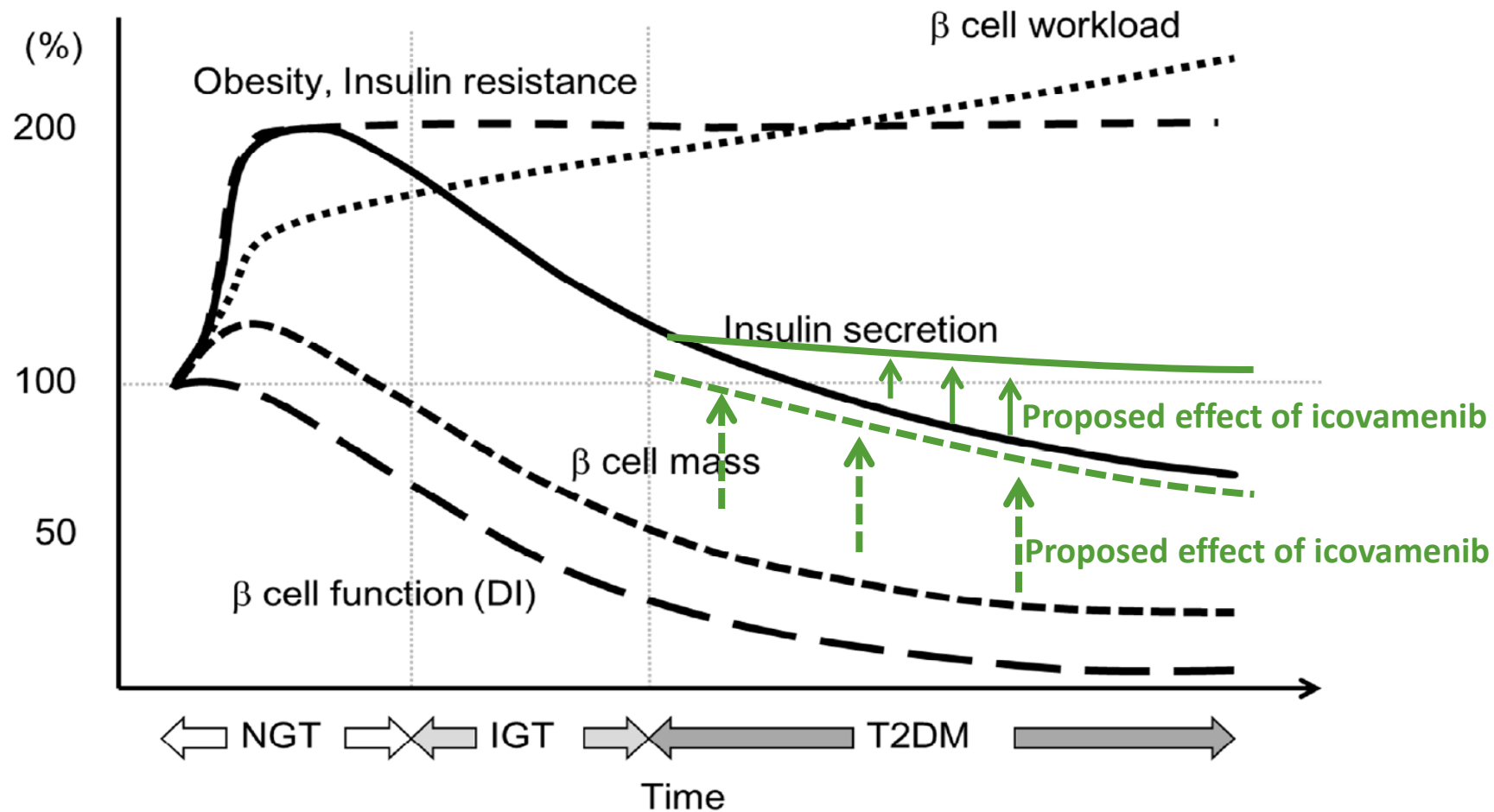


# Combination Treatment: Icovamenib Enhanced Responsiveness of Islets to Small Molecule GLP-1 RAs Orforglipron and BMF-650





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



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

### COVALENT-111 T2D MAD Cohorts

#### Eligibility Criteria

- T2D, age 18-65 yr
- Duration of diabetes 15 yr or less
- HbA<sub>1c</sub> 7.0 to 10.0%
- BMI 25 to 40 kg/m<sup>2</sup>
- 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

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

100 mg BID, without food  
x 4 weeks

200 mg QD  
x 2 weeks

400 mg QD  
x 2 weeks

without food

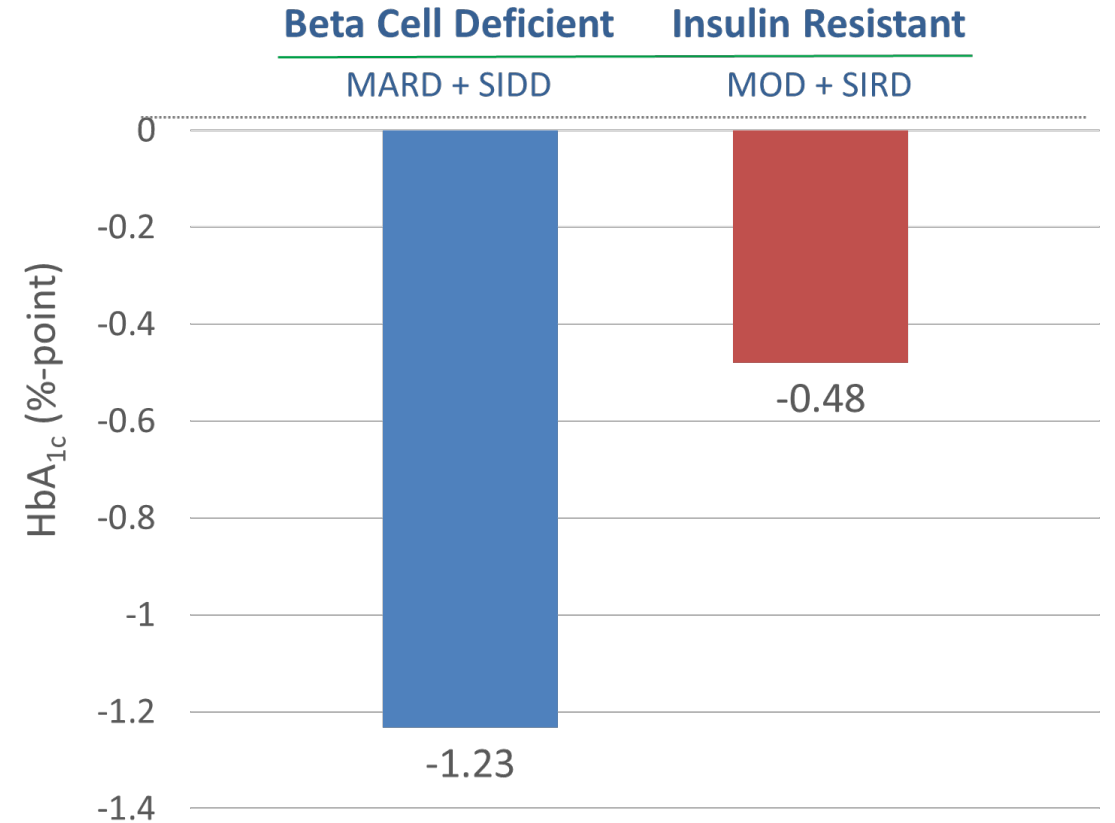
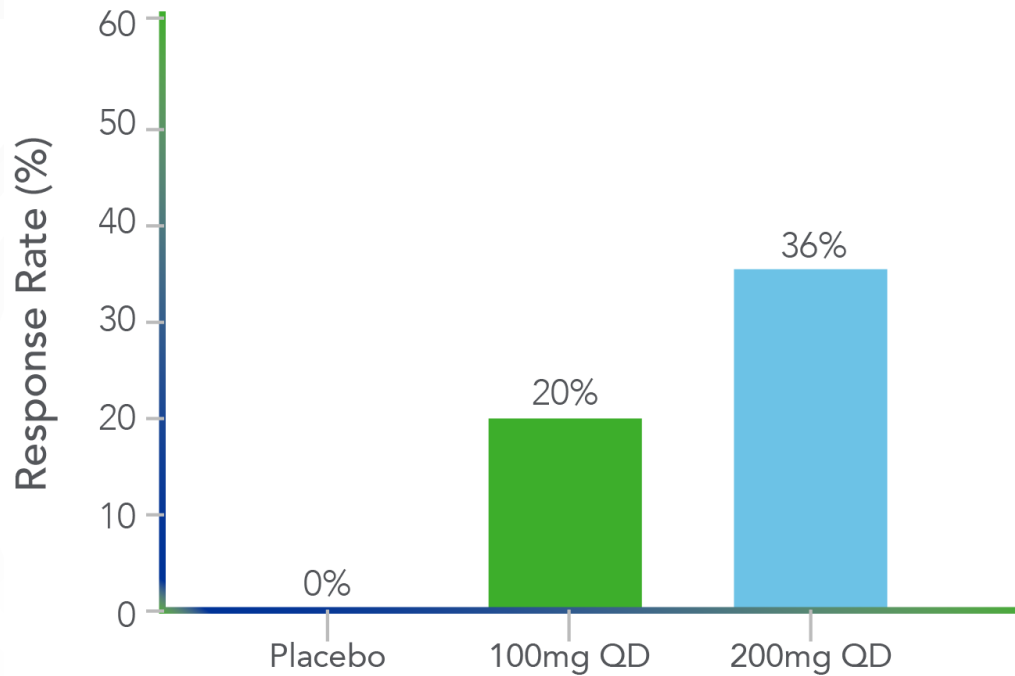
Icovamenib (n=10) and placebo (n=2) per cohort\*

\*200 mg with food cohort enrolled n=2 participants

4 weeks dosing + 22 weeks follow-up

# Proportion of patients with $\geq 1.0\%$ HbA<sub>1c</sub> reduction at Week 26 and change in HbA<sub>1c</sub> by T2D subtype

Response Rate, 100mg and 200mg



Placebo-adjusted change in HbA<sub>1c</sub> 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



Biomea Fusion

900 Middlefield Road, 4th floor

Redwood City, CA, 94063

[biomeafusion.com/diabetes-obesity](https://biomeafusion.com/diabetes-obesity)



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