Diabetes mellitus – advancing frontiers

6 Dec 2021

Scientific Paradigm Shifts Track (Part 1)

NMRC AWARDS CEREMONY AND RESEARCH SYMPOSIUM 2021

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Yishun Health

National Healthcare Group

Diabetes Mellitus – advancing frontiers

Outline

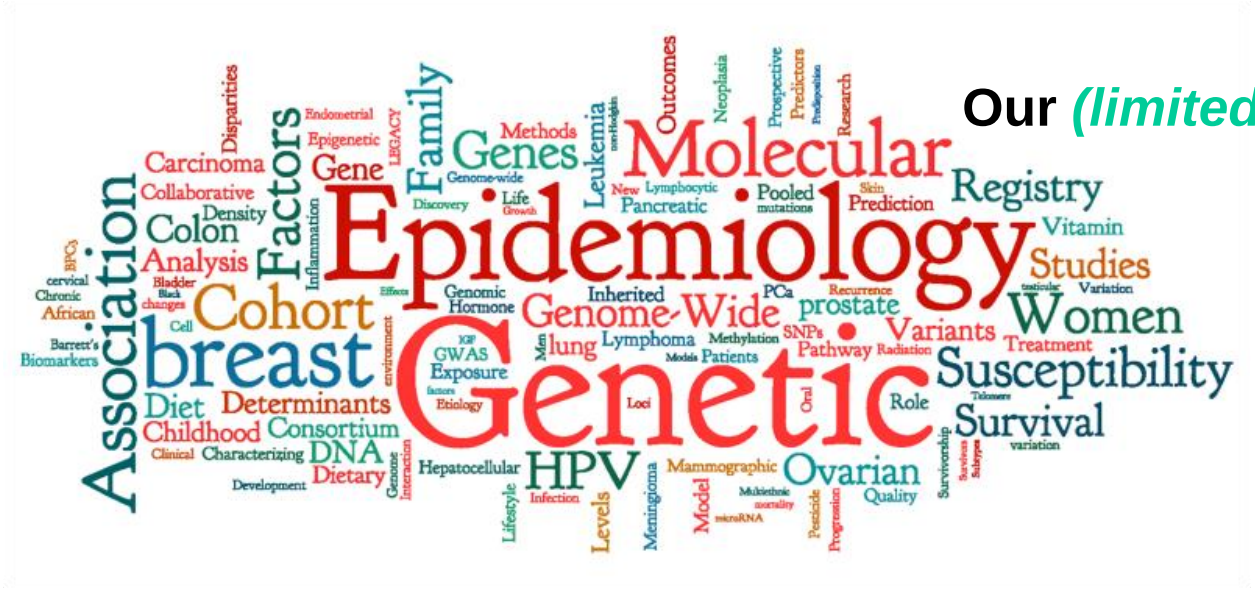
- Clinical epidemiology of diabetic kidney disease (DKD) – observations from our longitudinal cohorts.

- New frontiers in diabetes –
  - Disease modifying agents (SGLT2i & Incretins analogue),
  - Bariatric surgery and diabetes remission
  - Monogenic diabetes (precision diabetes),
  - Technologies (CGM & closed-loop hybrid insulin delivery)

- Summary

SGLT2i: Sodium–glucose co-transporter 2 inhibitors
CGM: Continuous Glucose Monitoring

Diabetic Kidney Disease (DKD)



Our *(limited)* experience

Distribution: e.g. disease prevalence

Determinants: i.e. causes

Metabolic Research at Yishun Health: 3 longitudinal diabetes cohorts

Diabetic Nephropathy (DN) Cohort

- Setup in **2002**
- ~5,800 hospital patients with diabetes, enriched with kidney disease
- Baseline blood and urine collected. Follow-up by EHR.

NMRC National Medical Research Council Singapore

SMART2D

2011: **S**ingapore Study of **M**acro-**a**ngiopathy and Micro-vascular **R**eactivity in **T**ype **2** **D**iabetes Cohort

- Setup in **2011**
- ~2,000 hospital & NHGP patients with type 2 diabetes
- Recall every 3 yearly
- Monitor multiple endpoints – vascular function, DKD, Diabetic foot syndrome, cognitive function.

Doris

Diabetic Kidney Disease Onset and Progression RISk Factors Cohort

- Setup in **2017**
- ~1,200 hospital ambulatory patients with diabetes
- Web-base dietary assessment, physical activity (wearable)
- Monitor DKD, NAFLD, 24 hour ambulatory BP

Study to identify genetic risk of kidney diseases

Members of the 10th Research, Innovation and Enterprise Council (RIEC), chaired by **Prime Minister Lee Hsien Loong**, meeting on Friday afternoon (July 21, 2017) to discuss the progress made on the RIE2020 plan launched in 2016.

{*From left to right*}: Prof Thomas Coffman, Prof Tai E Shyong, Prof Wong Tien Yin & A/Prof Lim Su Chi – **Theme PIs of DYNAMO.**

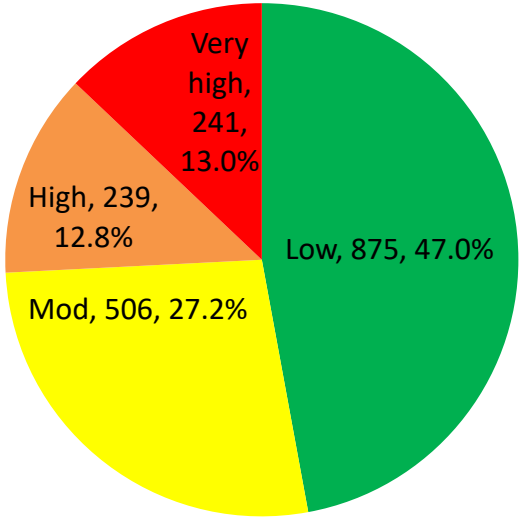
DYNAMO

Diabetes studY in Nephropathy And other Microvascular cOmplications

STRAITS TIMES PUBLISHED JUL 22, 2017, 5:00 AM SGT

$25m research effort aimed at spotting diabetic patients at risk so they can be treated earlier

DKD: Distribution by GFR and Albuminuria Categories (N=1861)



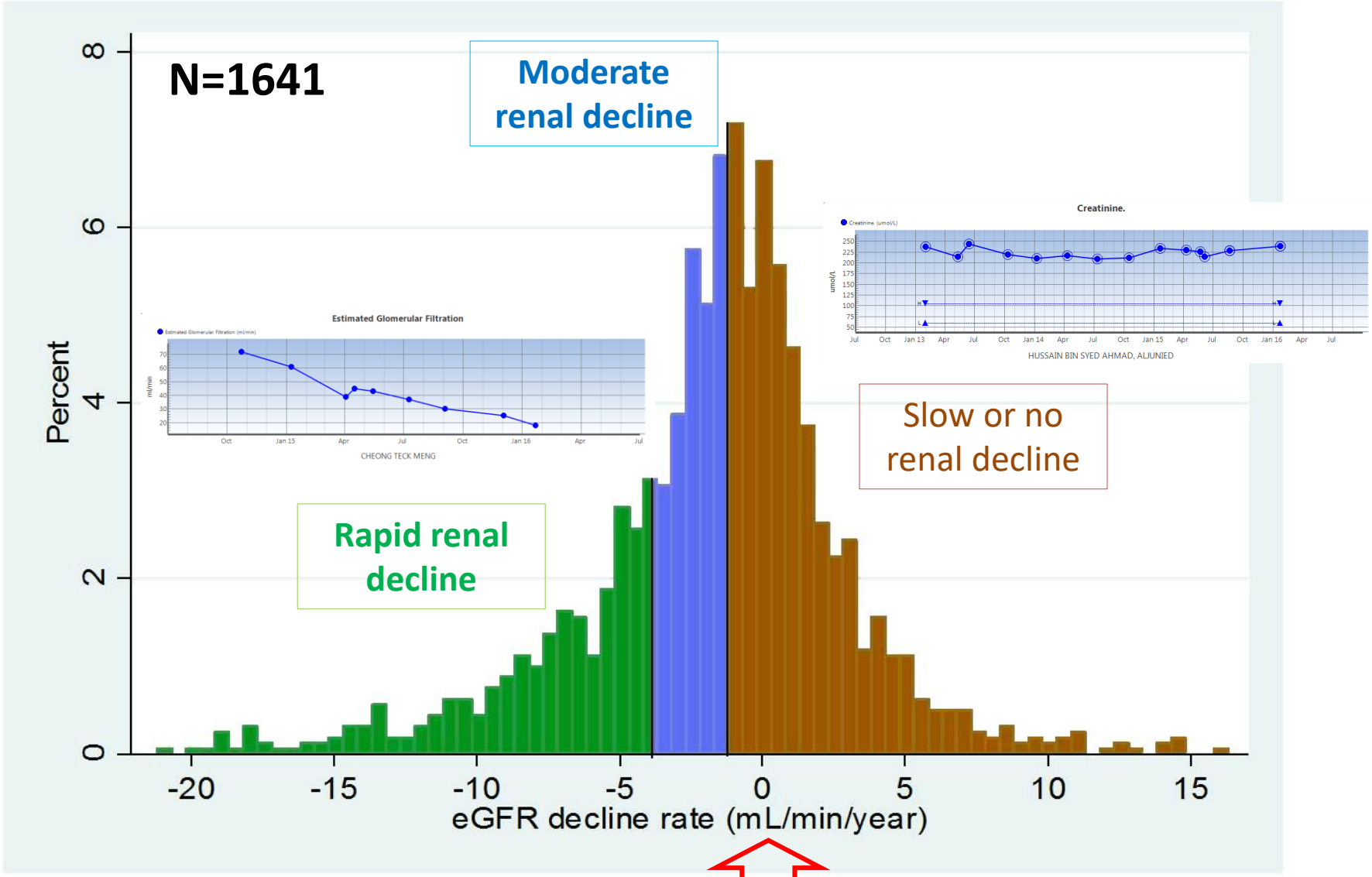
GFR categories (ml/min per 1.73 m²)				Persistent albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Mod increased	Severely increased
				<30mg/g	30-300mg/g	>300mg/g
	G1	Normal or high	≥90	469 (25)	256 (14)	55 (3)
	G2	Mildly decreased	60-89	406 (22)	188 (10)	88 (5)
	G3a	Mildly to mod decreased	45-59	62 (3)	68 (4)	49 (3)
	G3b	Mod to severely decreased	30-44	28 (2)	53 (3)	37 (2)
	G4	Severely decreased	15-29	3 (0)	19 (1)	48 (3)
	G5	Kidney failure	<15	0 (0)	1 (0)	31 (2)

Green: low risk; **yellow**: moderately increased risk; **orange**: high risk; **red**: very high risk

Low SK, Lim SC et al. Ann Acad Med Singapore. 2015;44:164-71

Khoo Teck Puat Hospital
Alexandra Health

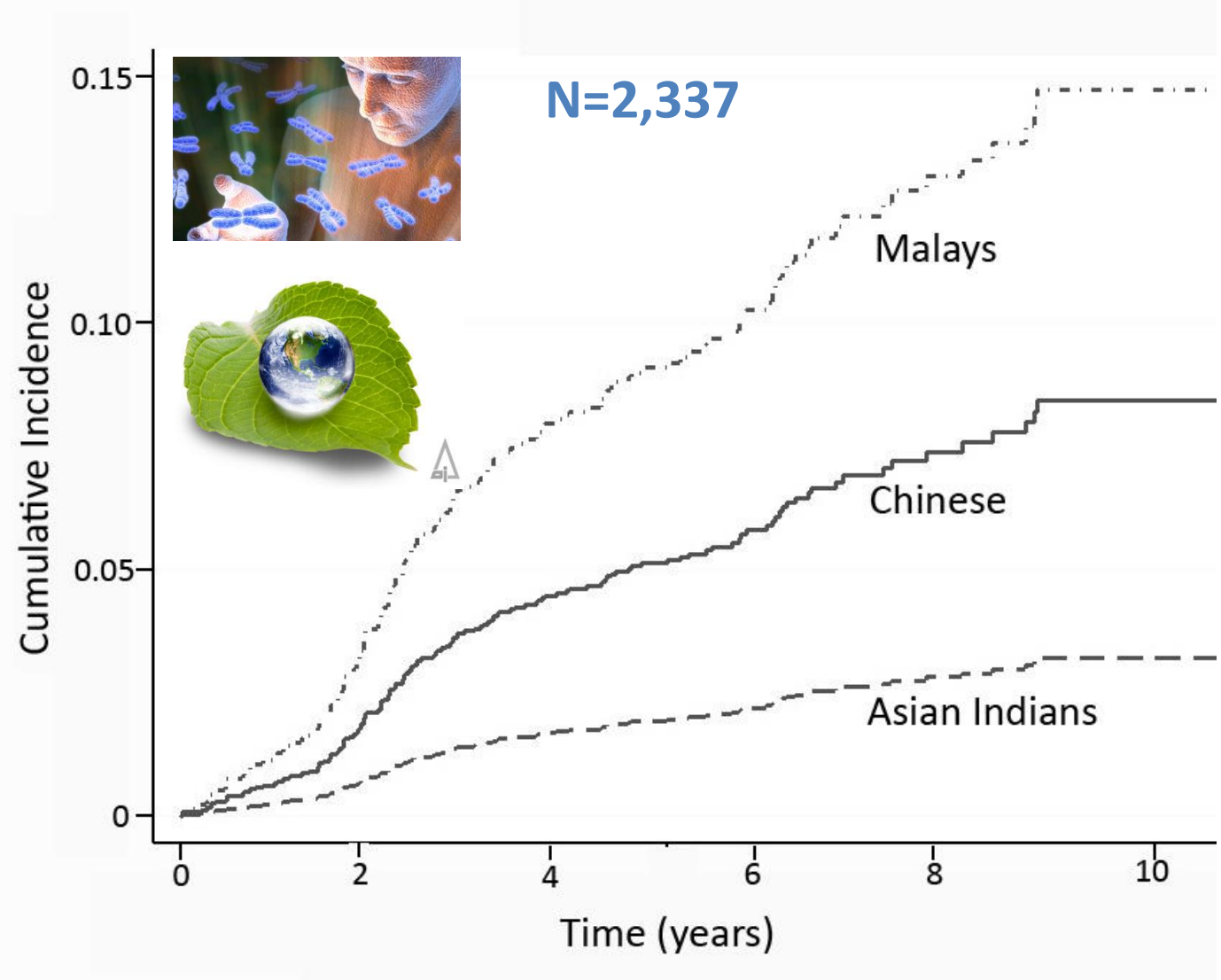
Heterogeneity in renal trajectory



SMART2D. Unpublished data

Khoo Teck Puat Hospital
Alexandra Health

Progression to ESRD by ethnicity



JJ Liu, SC Lim et al. Diabet. Med. 33, 332–339 (2016)

Calculator for Predicting Renal Progression in Patients with Type 2 Diabetes Mellitus

S Low & Lim SC et al. Diabetes Res Clin Pract. 2016;123:49-54

This is designed for adults with Type 2 Diabetes Mellitus

Variables at Baseline	Enter value
Urinary Albumin-to-Creatinine Ratio (mg/g)	300
HbA1c (%)	9
estimated glomerular filtration rate	45
Age (years)	70
Systolic BP (mmHg)	130
LDL-cholesterol (mmol/l)	4

	Training data set	Test data set
Total number of subjects	1107	475
Discrimination		
AUC (95% CI)	0.80 (0.77–0.83)	0.83 (0.79–0.87)
P	<0.001	<0.001
Calibration		
Hosmer-Lemeshow $\hat{C}$ test *P*	0.986	0.928
Sensitivity (%)	71.4 %	75.6%
Specificity (%)	72.2%	72.3%
PPV (%)	65.3%	68.9%
NPV (%)	77.4%	78.5%

Result **41.4%** ⇩ **of 100 people with this level of risk will have renal disease progression over a median duration of 5.5 years.**

Notes

1. Renal progression is defined as as eGFR decline as defined in the KDIGO 2012 Clinical Practice Guidelines – a decline in eGFR category [stage 1, ≥90 ml/min/1.73m2; stage 2, 60-89 ml/min/1.73m2; stage 3a, 45-59 ml/min/1.73m2; stage 3b, 30-44 ml/min/1.73m2;stage 4, 15-29 ml/min/1.73m2; and stage 5, <15 ml/min/1.73m2], coupled with a 25% or more reduction in eGFR from baseline.

2. The model is based on patients with CKD stages 1-4.

Reference

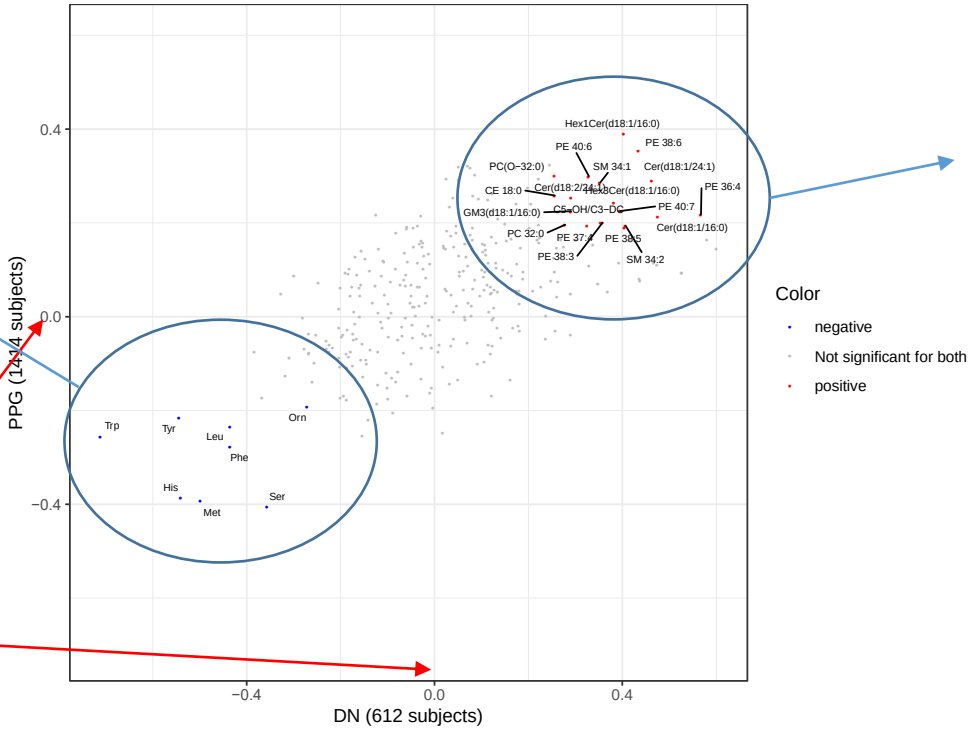
1. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 2014; 85: 49-61.

What metabolomics-signature is associated with > 30% ↓ in renal function (eGFR) among people with type 2 diabetes ?

Targeted Metabolomics: Regression Analysis with Adjustment for Confounders

Negative association
Amino acids

Positive association
PE / PC
Cer /SM / Hex1Cer



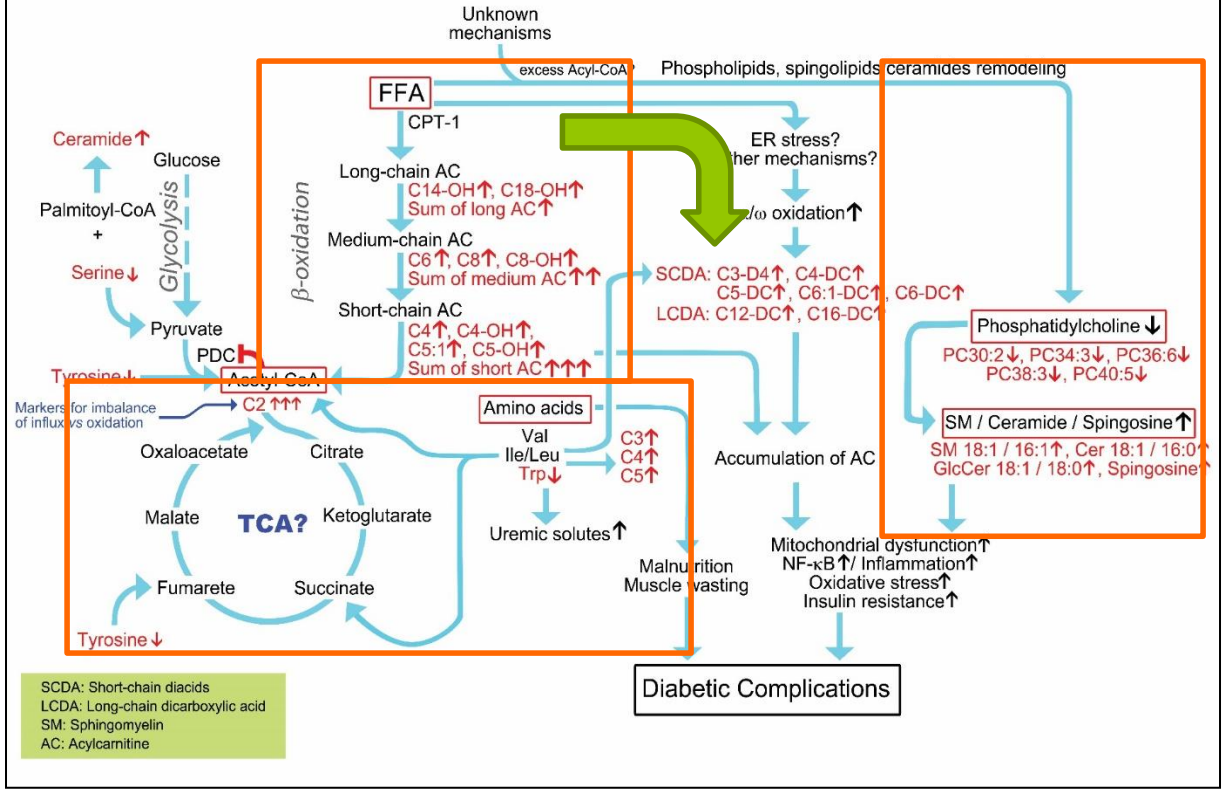
Log odds of steep decline (per stdev in compound)

PE: Phosphatidylethanolamine
PC: Phosphatidylcholine
Cer: Ceramindes
SM: Sphingomyelin

- Δ eGFR < -30% ~ Compound + Age + Gender + Ethnicity + DM Duration + eGFR baseline
- Subjects with baseline eGFR < 60 were removed

Unpublished preliminary data
Courtesy of A/Prof Choi Hyung Won, NUHS

Summary of cross-sectional targeted plasma metabolomics study



Liu & Lim et al. Kidney Int Rep (2017) 2, 470–480

In Asian patients with T2DM and DKD, we observed:

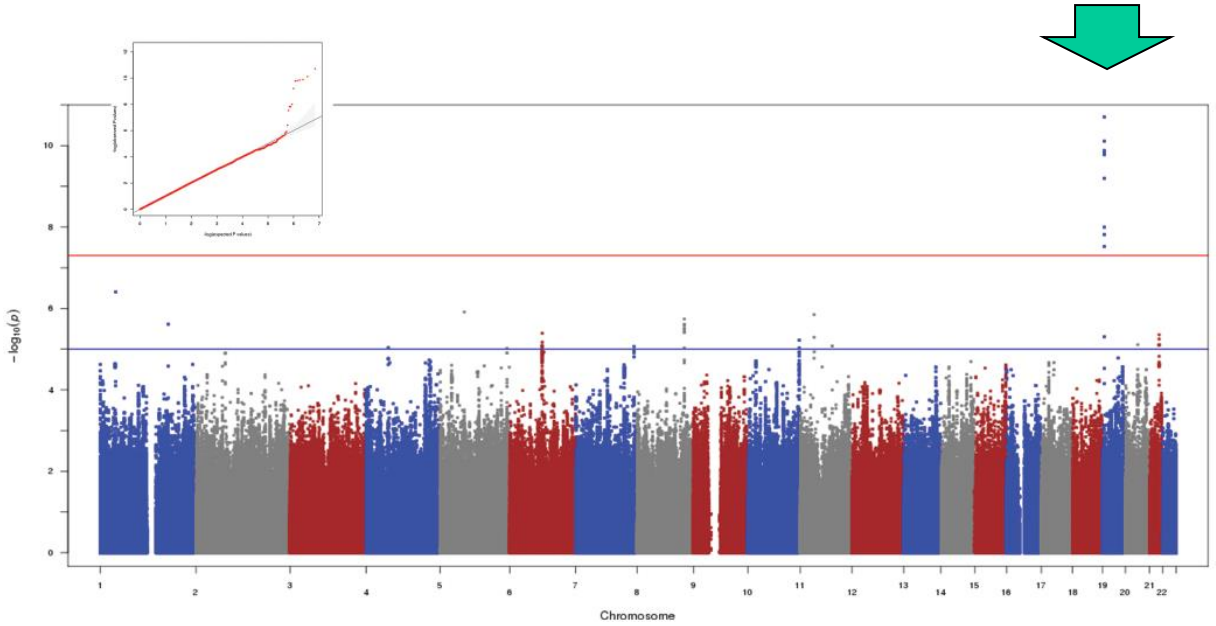
- ↑ Even-chain acylcarnitine, ↑ dicarboxylic acylcarnitine suggest incomplete fatty acid β-oxidation (FAO) and shunting to ω-oxidation i.e. mismatch (supply & demand) substrate flux and utilization in mitochondria
- ↑ ↓ plasma phosphatidylcholine levels and ↑ long-chain sphingomyelin and ceramide levels suggested remodeling of sphingolipids→ pro-inflammatory milieu
- ↑ Short chain acylcarnitine suggests accelerated catabolism of amino acids i.e. altered energy substrate selection

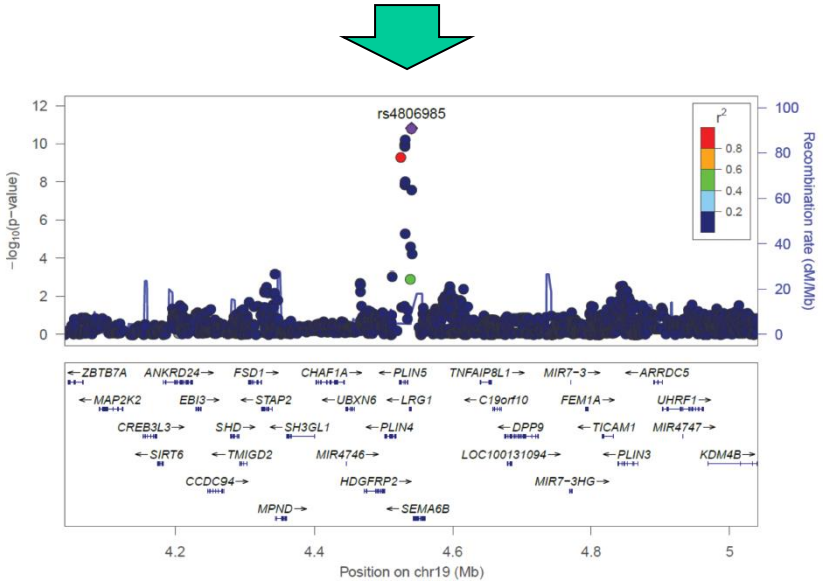
To follow-up on mitochondria dysfunction, we study whether urine TCA cycle metabolites were associated with progressive CKD in patients with T2DM

Causal Inference by
Mendelian Randomization (MR) de-confounding

Association of genetic variants for plasma LRG1 with rapid decline in kidney function in patients with type 2 diabetes.

Resham L GURUNG, Rajkumar DORAJOO, Yiamunaa M, Jian-Jun LIU , Sharon Li Ting PEK, Jiexun WANG , Ling WANG , Xueling SIM , Sylvia LIU, Yi-Ming SHAO, Keven ANG, Tavintharan SUBRAMANIAM, Wern E TANG, Chee Fang SUM , Jian-Jun LIU, and Su Chi LIM.





J Clin Endocrinol Metab 2021;106:2384–2394.

New frontiers in diabetes

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - **2018**

Diabetes Care 2018;41(Suppl. 1):S73–S85

American Diabetes Association®

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

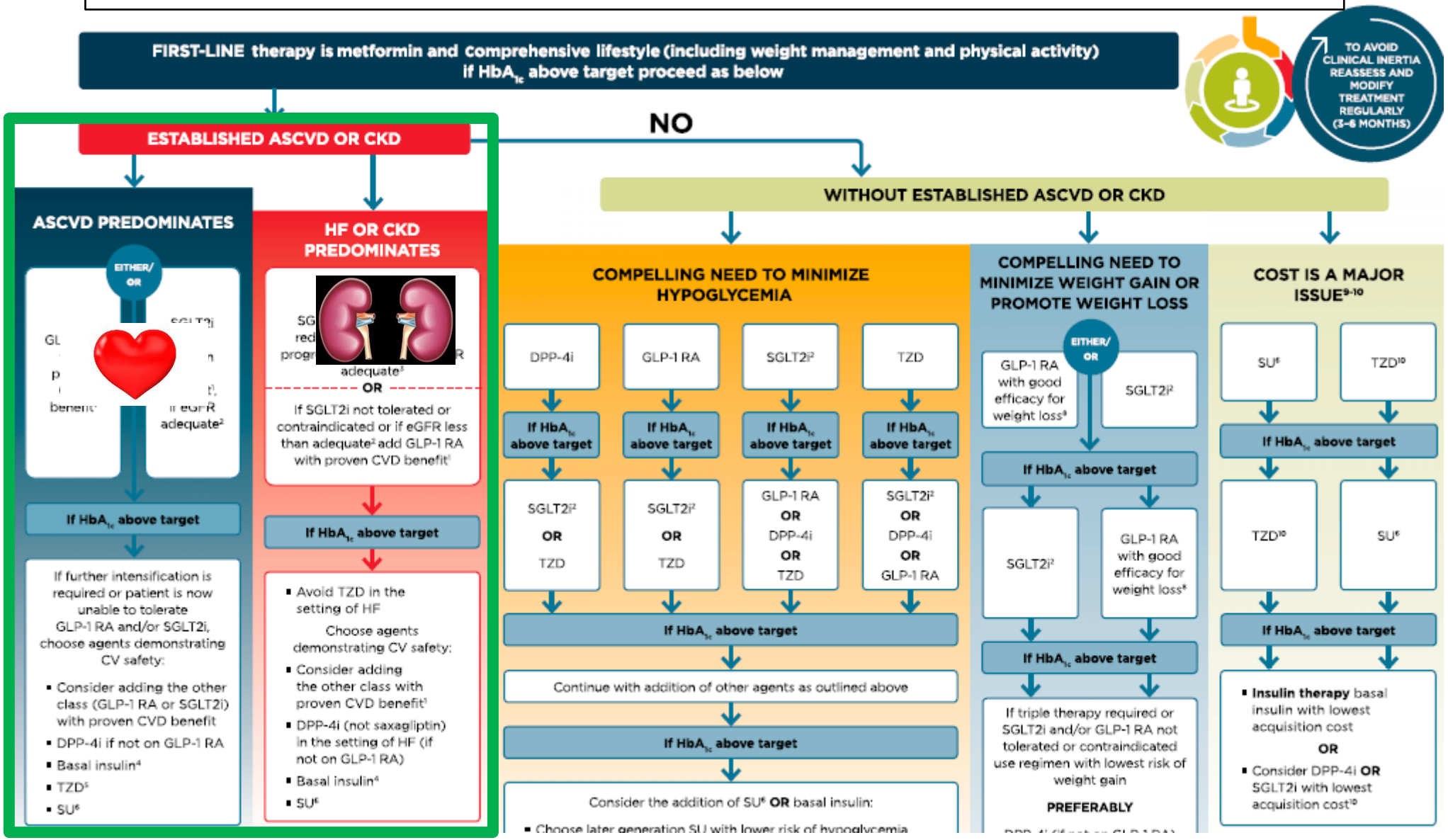
Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

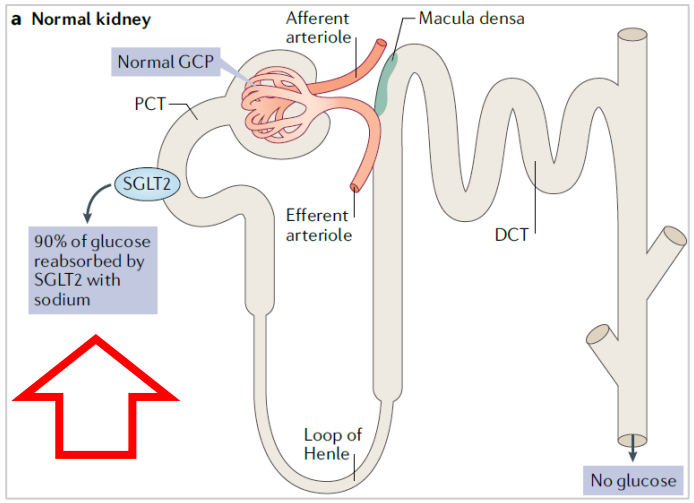
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - **2019**

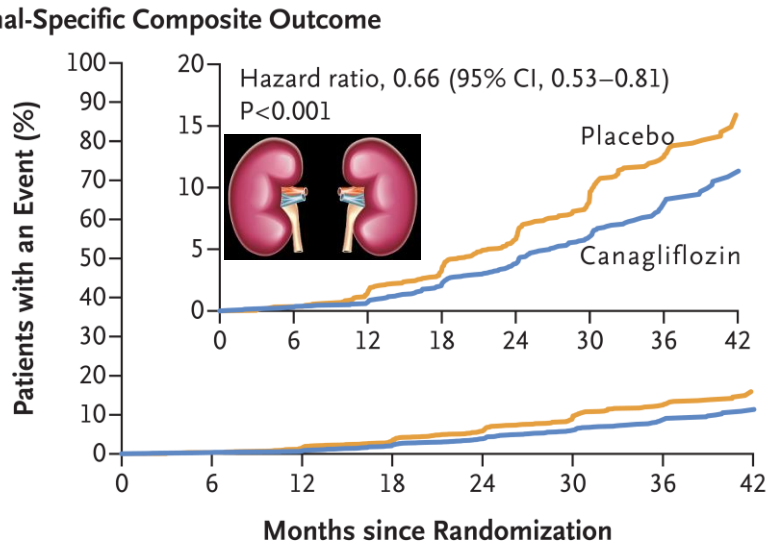
Diabetes Care 2019;42(Suppl. 1):S90–S102

American Diabetes Association®

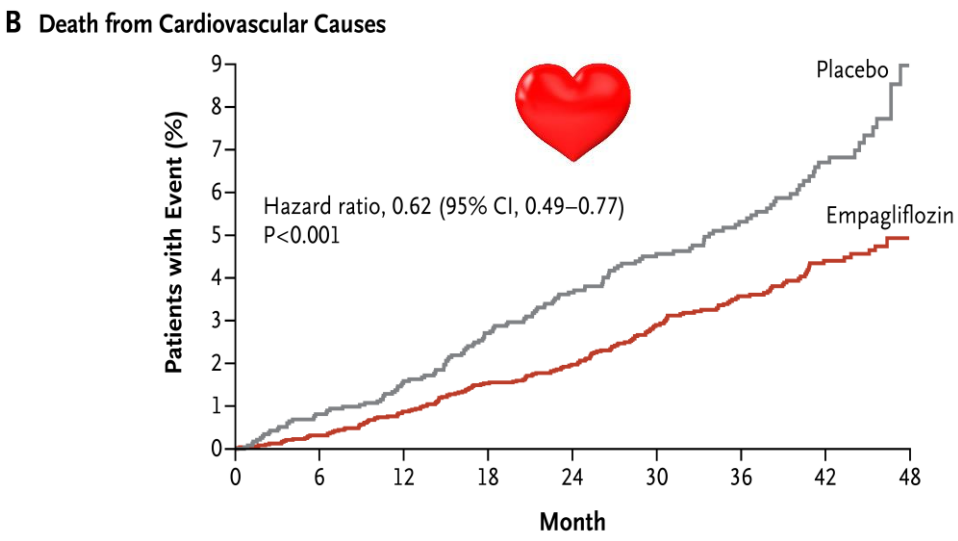


Sodium–glucose co-transporter 2 (SGLT2) inhibitors and Cardio-renal Outcomes in Type 2 Diabetes & Nephropathy



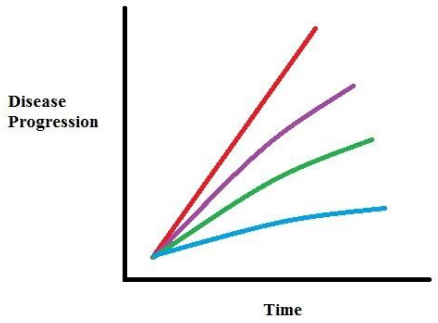


No. at Risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes



EMPA-REG NEJM 2015;373:2117-28; **CREDENCE** DOI: 10.1056/NEJMoa1811744; 2019; DAPA-CKD NEJM 2021.

Incretins (gut hormones) - Glucagon-like peptide 1 in health and disease

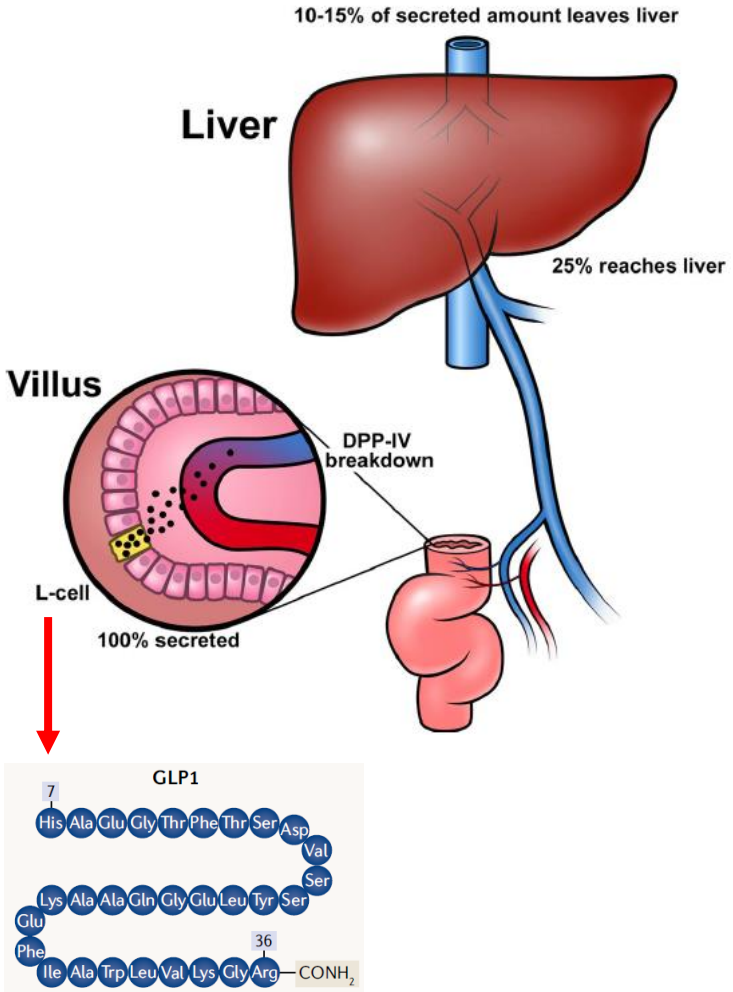
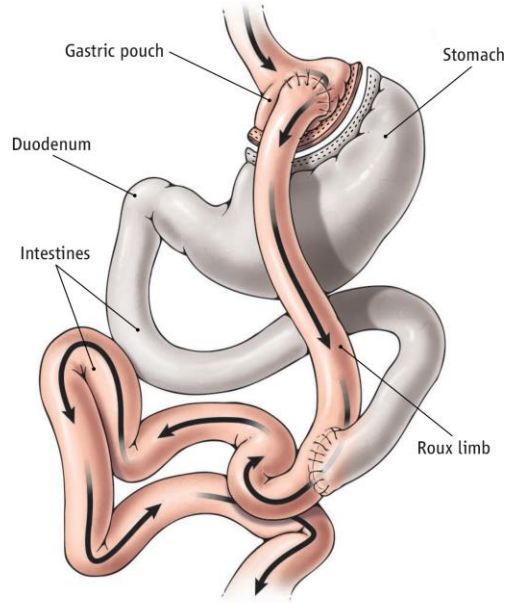


Figure 3: **All-cause mortality, hospital admission for heart failure, and kidney outcomes**

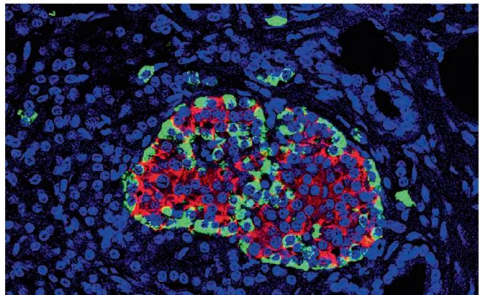
Nature Reviews | Endocrinology **2018**

Remission of diabesity (type 2 diabetes)

Bariatric Surgery cohort (OMICS)



Unintended effects. Roux-en-Y gastric bypass surgery reduces the stomach to a fraction of its original size and skips past part of the small intestine, which causes profound metabolic changes in the gut.



An adult human islet.
Red colour shows insulin
green shows glucagon
blue shows nuclei

OMICS: Obesity Metabolic Intervention Cohort Study

Science. 2008 ;320:438-40; S4 | Nature Milestones | Diabetes | June 2021

Obes Surg. 2020 Sep;30(9):3387-3393. doi: 10.1007/s11695-020-04576-3.

Metabolic Surgery Diabetes Remission (MDR) Score a New Preoperative Scoring System for Predicting Type 2 Diabetes Remission at 1 Year After Metabolic Surgery in the Singapore Multi-ethnic Asian Setting

Mei Chung Moh [1], Anton Cheng [2], Chun Hai Tan [2], Boon Khim Lim [1], Bo Chuan Tan [2], Deborah Ng [2], Chee Fang Sum [3], Tavintharan Subramaniam [1 3], Su Chi Lim [4 5 6]

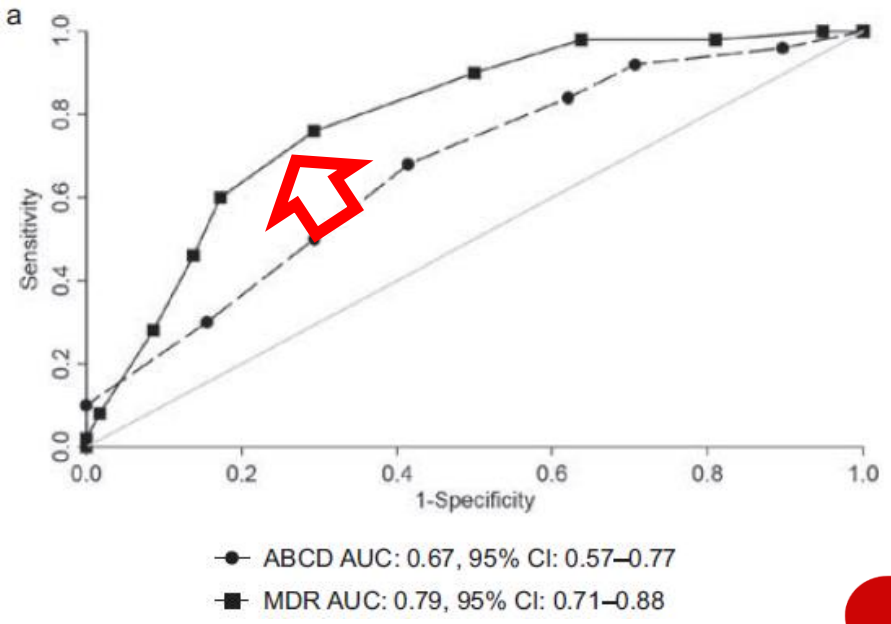
Table 1 Baseline subject characteristics subgrouped by diabetes remission status post-metabolic surgery

Variable	Total ($n = 114$)	Non-remitters ($n = 60$)	Remitters ($n = 54$)	*P* value
Age (years)	46 ± 9	48 ± 10	44 ± 8	0.013
Men, *n* (%)	55 (48.2)	24 (40.0)	31 (57.4)	0.063
Ethnicity, *n* (%)				
Chinese	37 (32.4)	21 (35.0)	16 (29.6)	0.659
Malay	46 (40.4)	25 (41.7)	21 (38.9)	
Indian	20 (17.5)	8 (13.3)	12 (22.2)	
Others	11 (9.6)	6 (10.0)	5 (9.3)	
BMI (kg/m^2)	40.1 ± 6.6	39.9 ± 7.2	40.3 ± 5.9	0.736
FPG (mmol/L)[a]	9.7 ± 3.7	10.6 ± 3.7	8.6 ± 3.3	0.005
HbA1c (%)	8.8 ± 1.9	9.4 ± 2.0	8.1 ± 1.6	< 0.001
Diabetes duration (years)	6 (2–10)	9 (6–12)	3 (1–6)	< 0.001
Hypertension, *n* (%)	89 (78.1)	47 (78.3)	42 (77.8)	0.943
Hyperlipidaemia, *n* (%)	98 (86.0)	57 (95.0)	41 (75.9)	0.003
C-peptide (ng/ml)	3.1 (2.0–3.9)	2.7 (1.6–3.9)	3.3 (2.3–3.9)	0.136
HOMA-IR[a]	2.7 (1.7–3.6)	2.6 (1.6–3.8)	2.7 (1.9–3.2)	0.882
HOMA-B (%)[a]	55.0 (27.0–90.6)	42.0 (22.9–87.1)	76.8 (43.0–107.5)	0.005
Medications, *n* (%)				
OHGA	103 (90.4)	54 (90.0)	49 (90.7)	0.894
Insulin	42 (36.8)	33 (55.0)	9 (16.7)	< 0.001
Anti-hypertensives	75 (65.8)	42 (70.0)	33 (61.1)	0.318
Lipid-lowering	85 (74.6)	52 (86.7)	33 (61.1)	0.002
Surgery, *n* (%)				
RYGB	80 (70.2)	38 (63.3)	42 (77.8)	0.092
SG	34 (29.8)	22 (36.7)	12 (22.2)	

BMI, body mass index; *FPG*, fasting plasma glucose; *HOMA-IR*, homeostasis model assessment of insulin resistance; *HOMA-B*, homeostasis model assessment of β-cell function; *OHGA*, oral hypoglycaemic agent; *RYGB*, Roux-en-Y gastric bypass; *SG*, laparoscopic sleeve gastrectomy

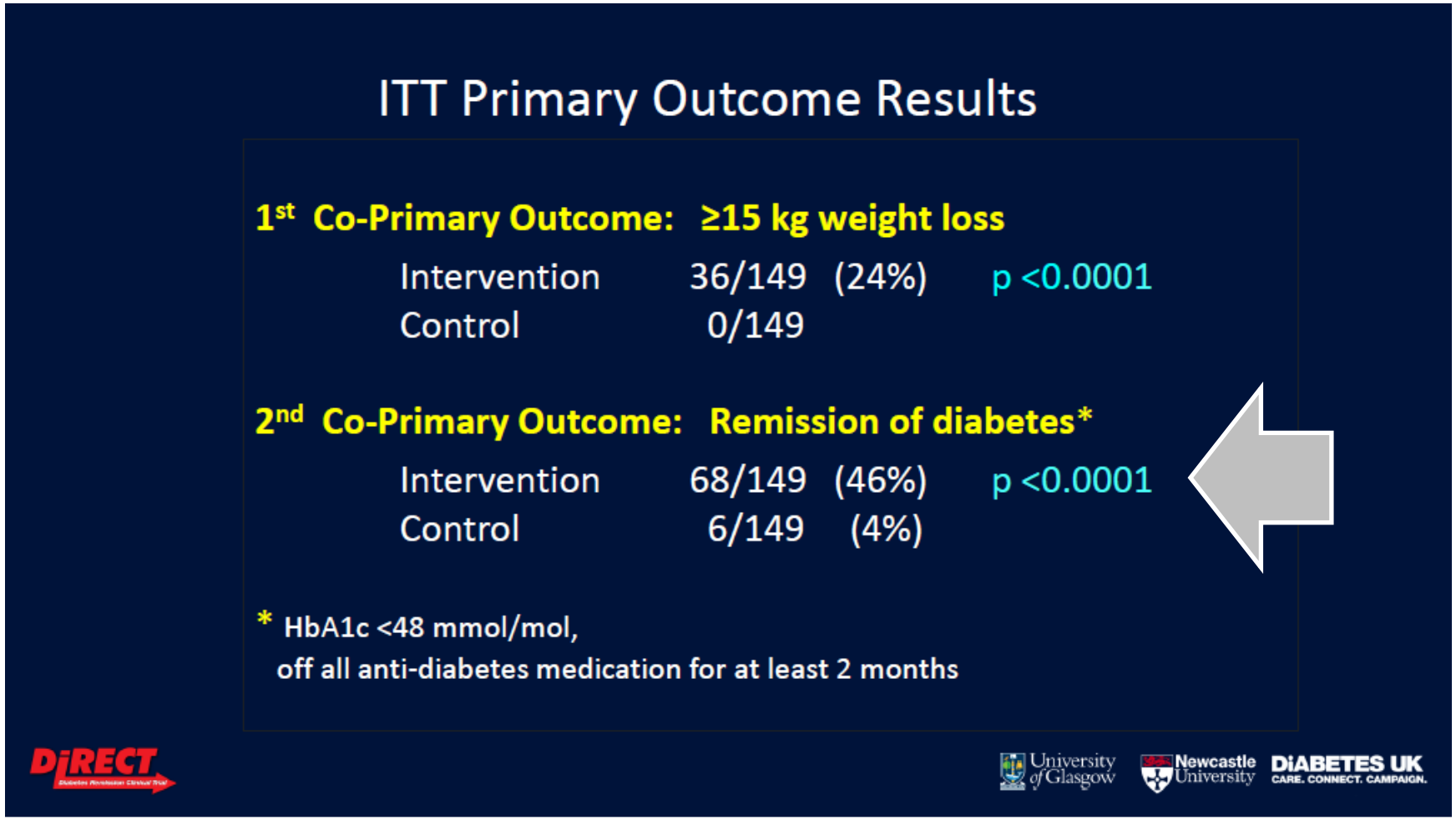
Table 3 Variables and score used to calculate MDR

MDR	0	1	2	3
Age (years)	> 50	41–50	≤ 40	-
HOMA2-B (%)	≤ 40	> 40–80	> 80	-
DM duration (years)	≥ 10	6–9	2–5	< 2
HbA1c (%)	≥ 10	8.5–< 10	7.0–< 8.5	< 7



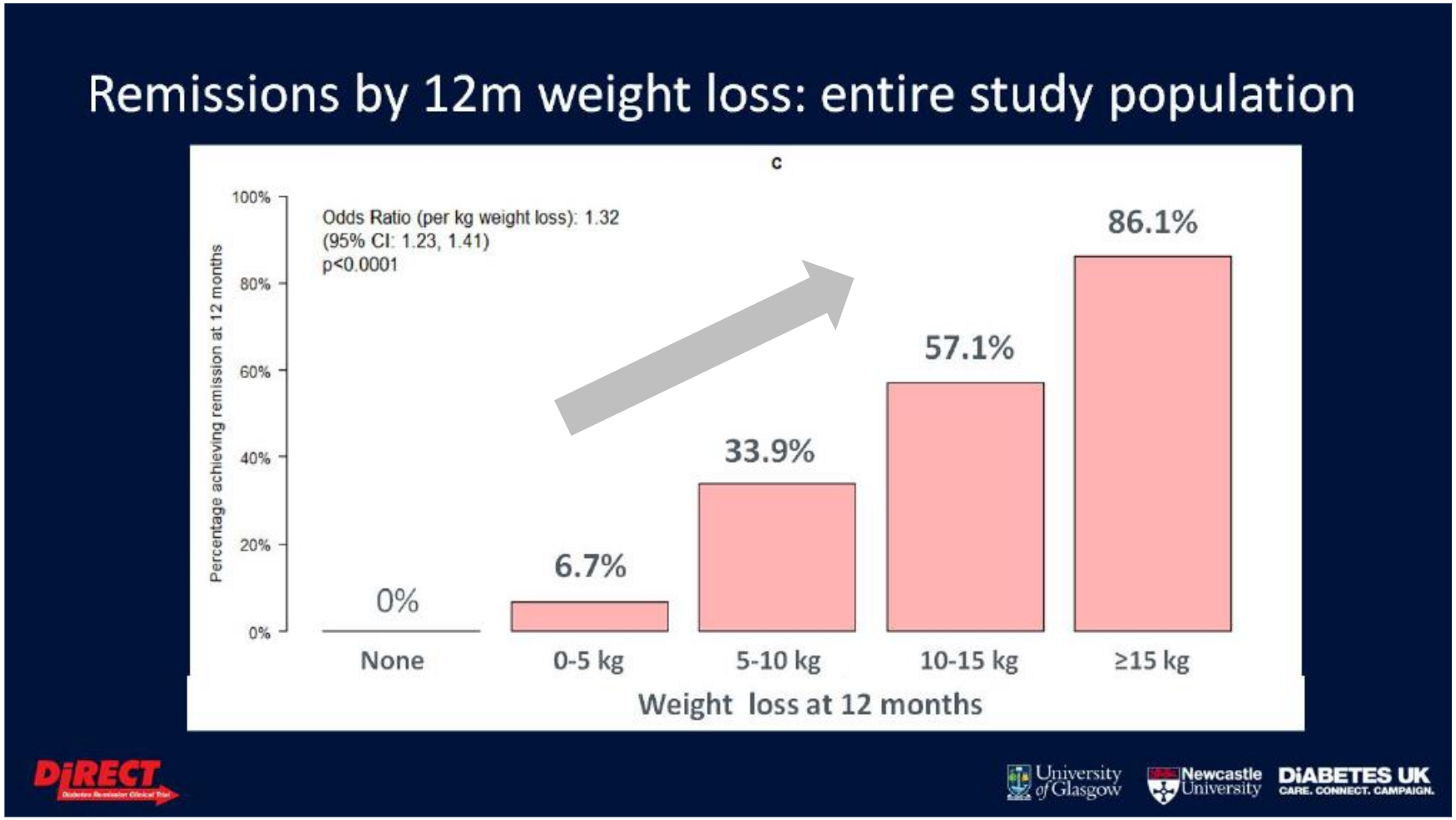
OMICS: Obesity Metabolic Intervention Cohort Study

Durability of a primary care-led non-surgical (VLCD) weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial



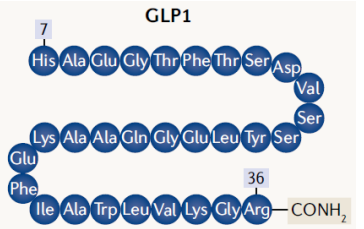
Lancet Diabetes Endocrinol 2019; 7: 344–55

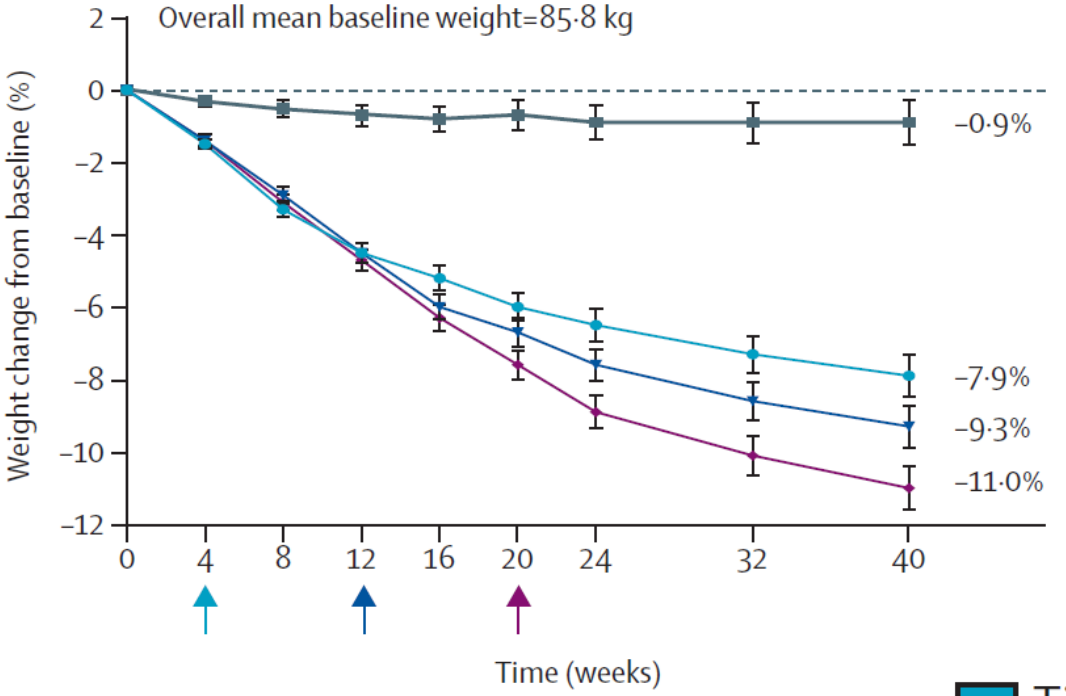
Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial

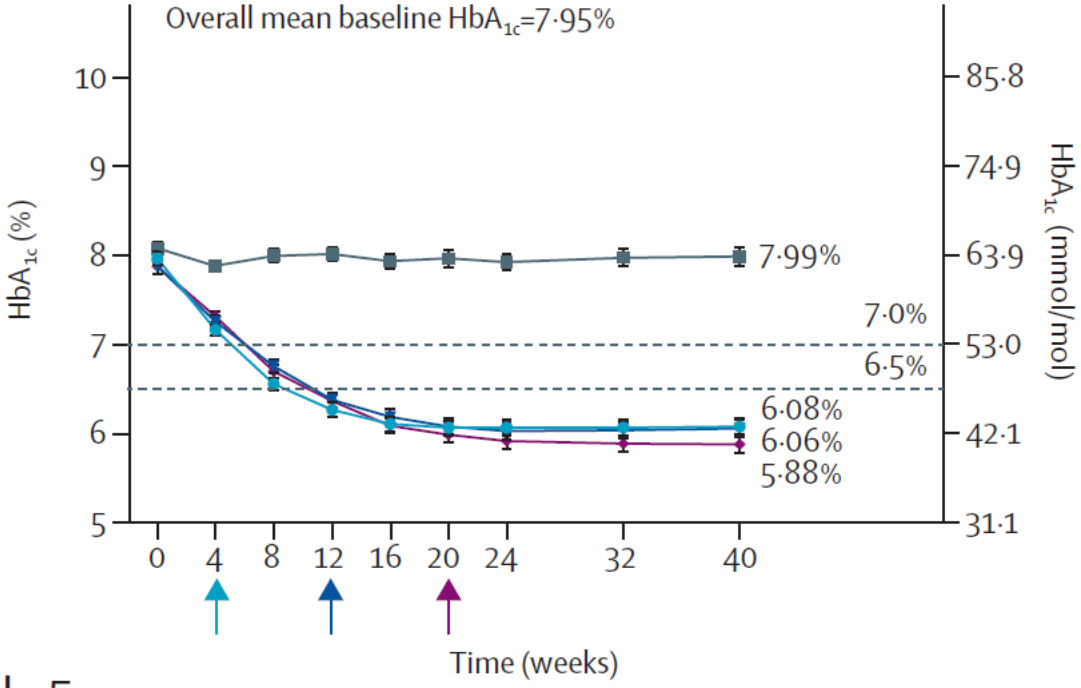


Lancet Diabetes Endocrinol 2019; 7: 344–55

Incretins in obesity and diabetes







Tirzepatide 5mg
Tirzepatide 10mg
Tirzepatide 15mg
Placebo

Incretin drugs in diabetic kidney Disease. Nature Reviews | Nephrology 2020; Lancet 2021; 398: 143–55

Monogenic subset of people with complex traits DHLO.

National Precision Medicine Initiative

PRECISE
Precision Health Research Singapore

DHLO

Diabetes
Hypertension
Hyper-**L**ipidaemia
Obesity

MONOGENIC DIABETES REGISTRY

MONOGENIC HYPERTENSION RESEARCH

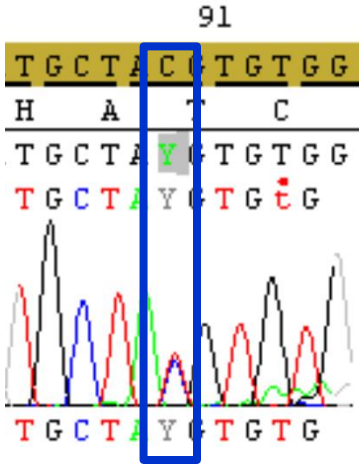
FHCARE

Familial hypercholesterolemia

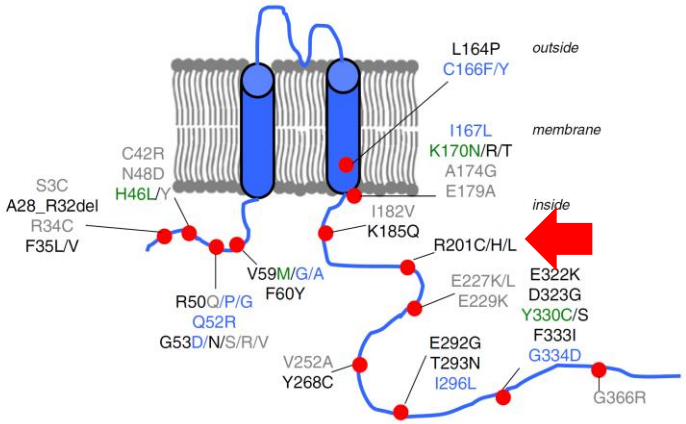
OMICS
Obesity – Metabolism & Intervention Cohort Study

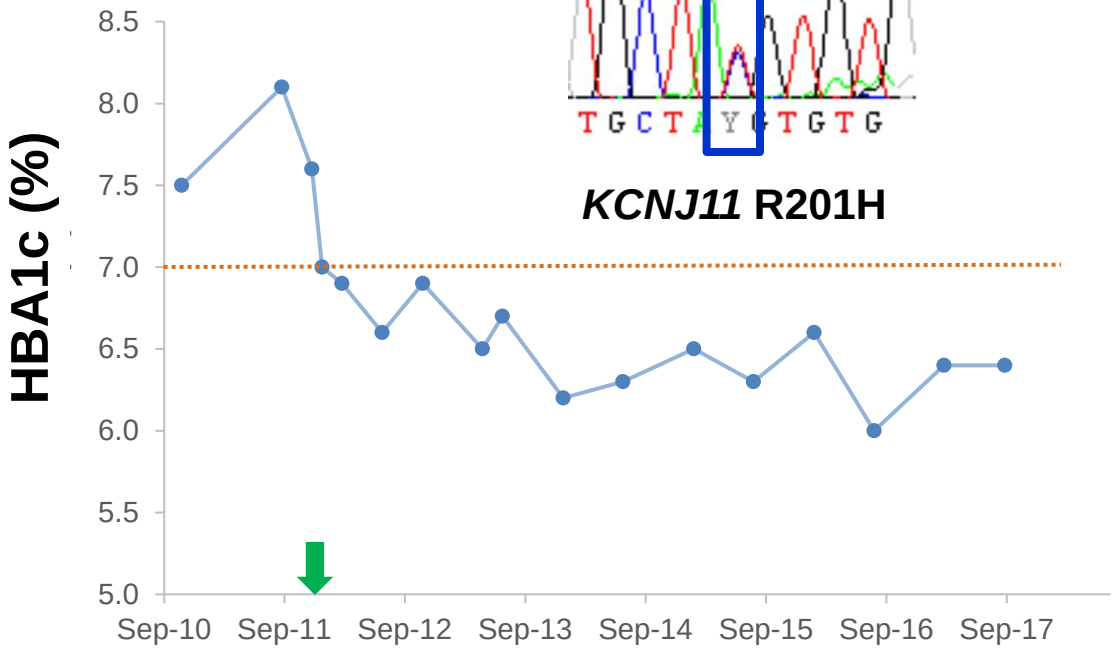
Monogenic obesity

- A non-trivial subset of individuals with complex trait (e.g. DHLO) can be attributable to a monogenic condition (e.g. FH and MODY).
- Monogenic disease are individually rare but collectively abundant.
- They consume healthcare disproportionally (20/80 rule).
- They are the low-hanging fruits for genomic medicine i.e. targeted therapy with good results may be possible.
- They shed light on disease biology.



***KCNJ11* R201H**





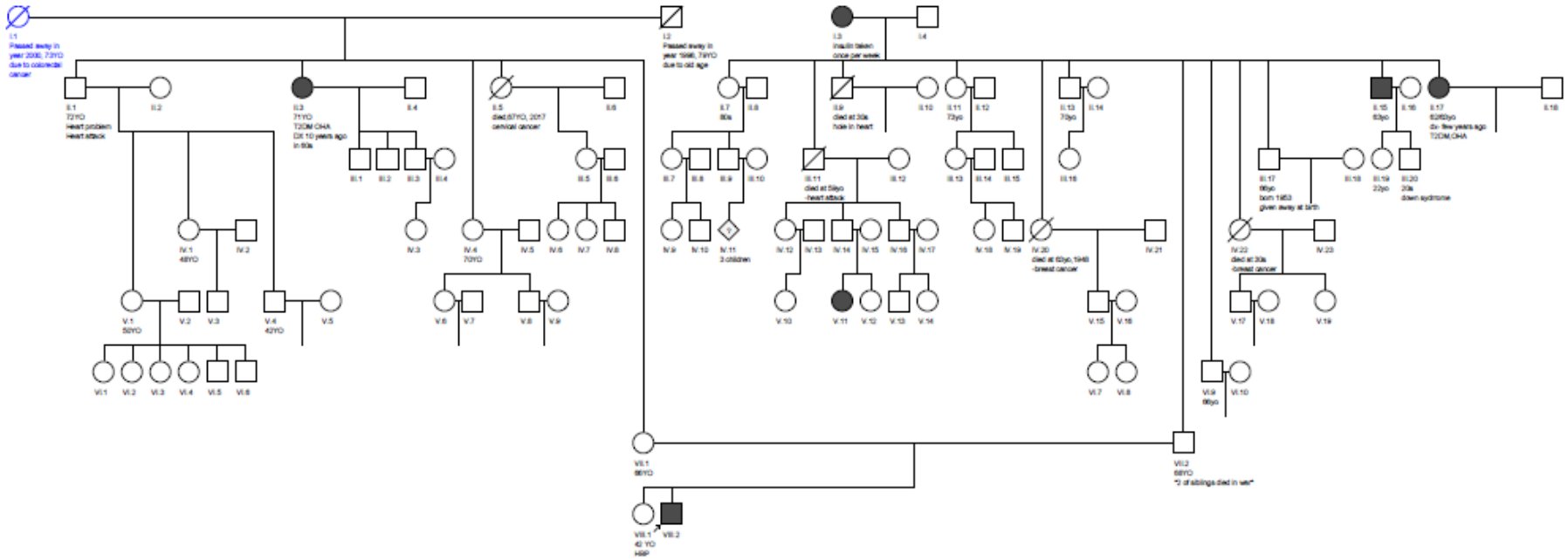
64u/day → Glibenclamide 65 mg/day → Glibenclamide 22.5 mg/day

Hypoglycemia

Ang SF, Lim SC et al. European J of Hum Gen (2019) 27:989–993

Family Cascade

Race	Gender	Age of Onset	Family Hx[1]	BMI (kg/m^2)	Insulin treatment	OHA treatment	HbA1c (%)	HNF1B mutation	CKD-Epi-eGFR (ml/min/1.73m^2)	Diagnostic delay
Chinese	M	23	Yes	17.2	Glargine 14U ON (still giving 16), Glulisine 4U TDS (still giving 6U for lunch and dinner only)	Nil	7.3	Whole-gene deletion	92	10 years



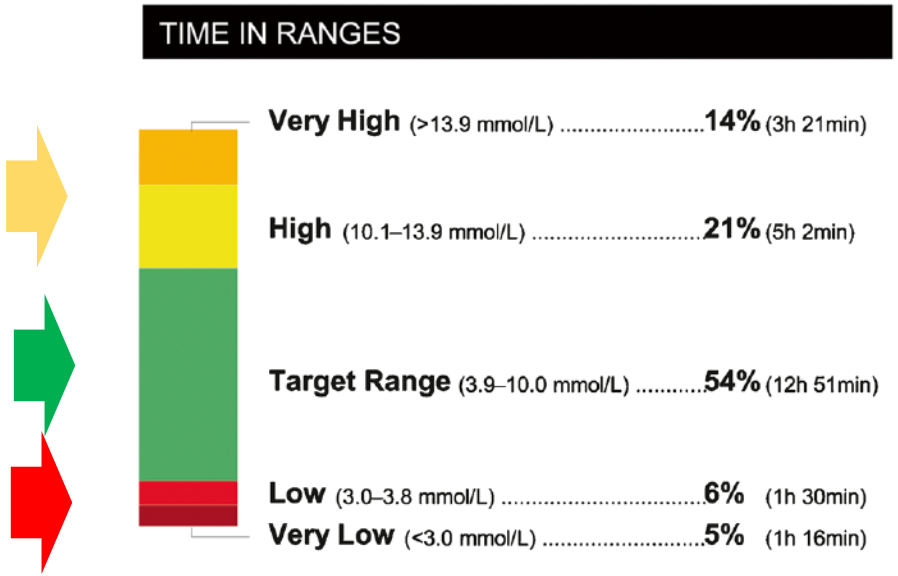
The *FreeStyle Libre* System provides more than just a glucose number

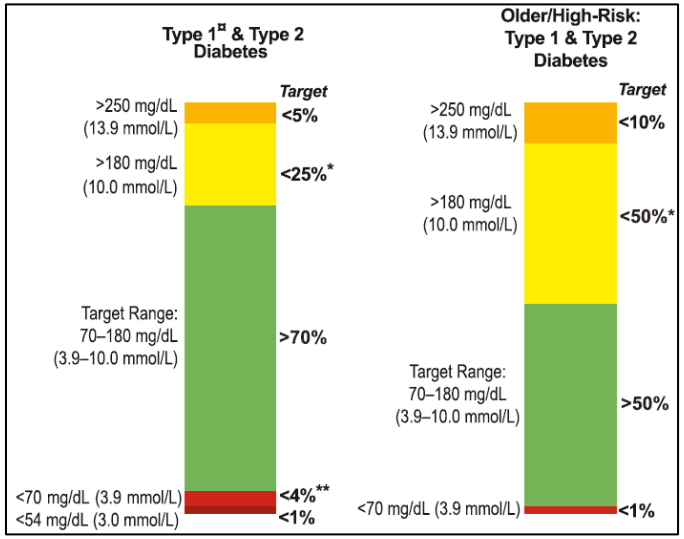
Reader display after a scan

Current Glucose reading

Glucose Trend Arrow
Direction and rate glucose is heading

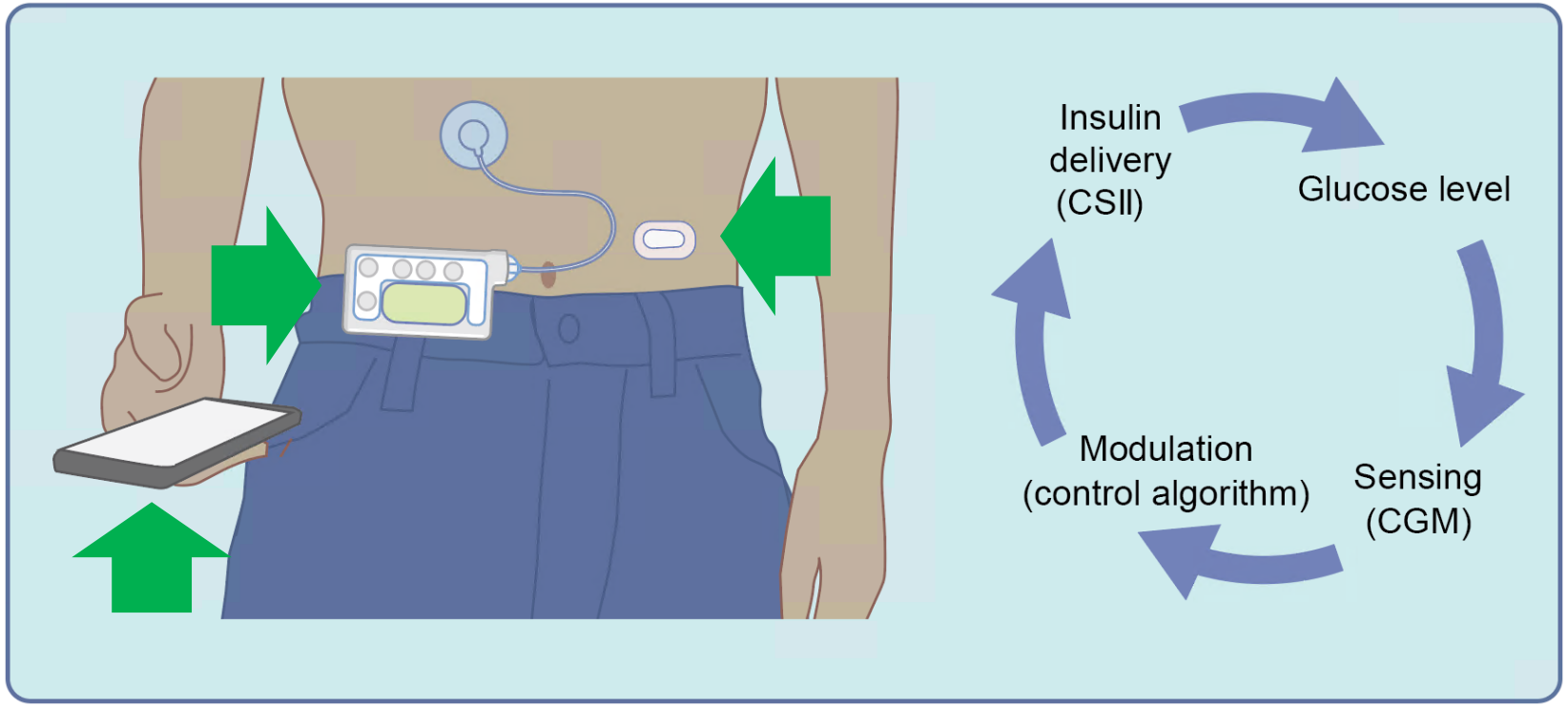
Glucose history





Diabetologia (2020) 63:242–252
Diabetes Care 2019;42:1593–1603

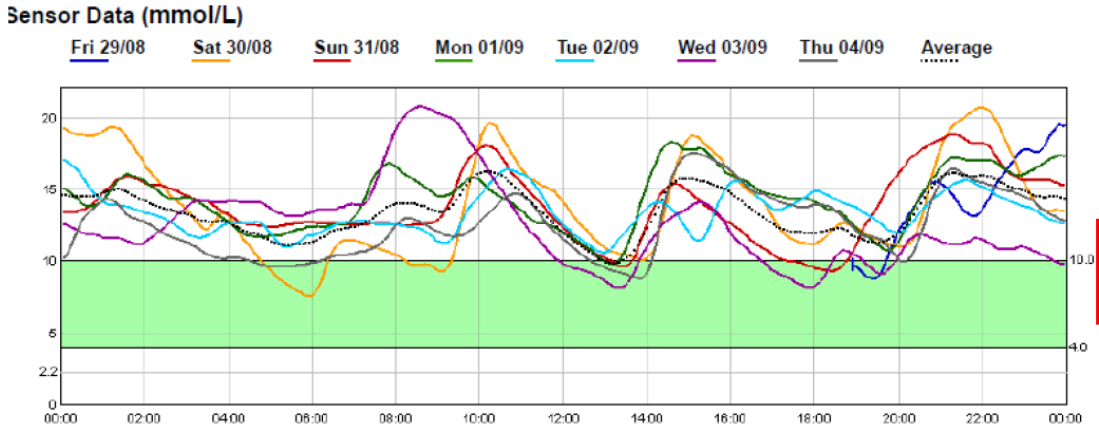
Schematic of the configuration of closed-loop insulin delivery

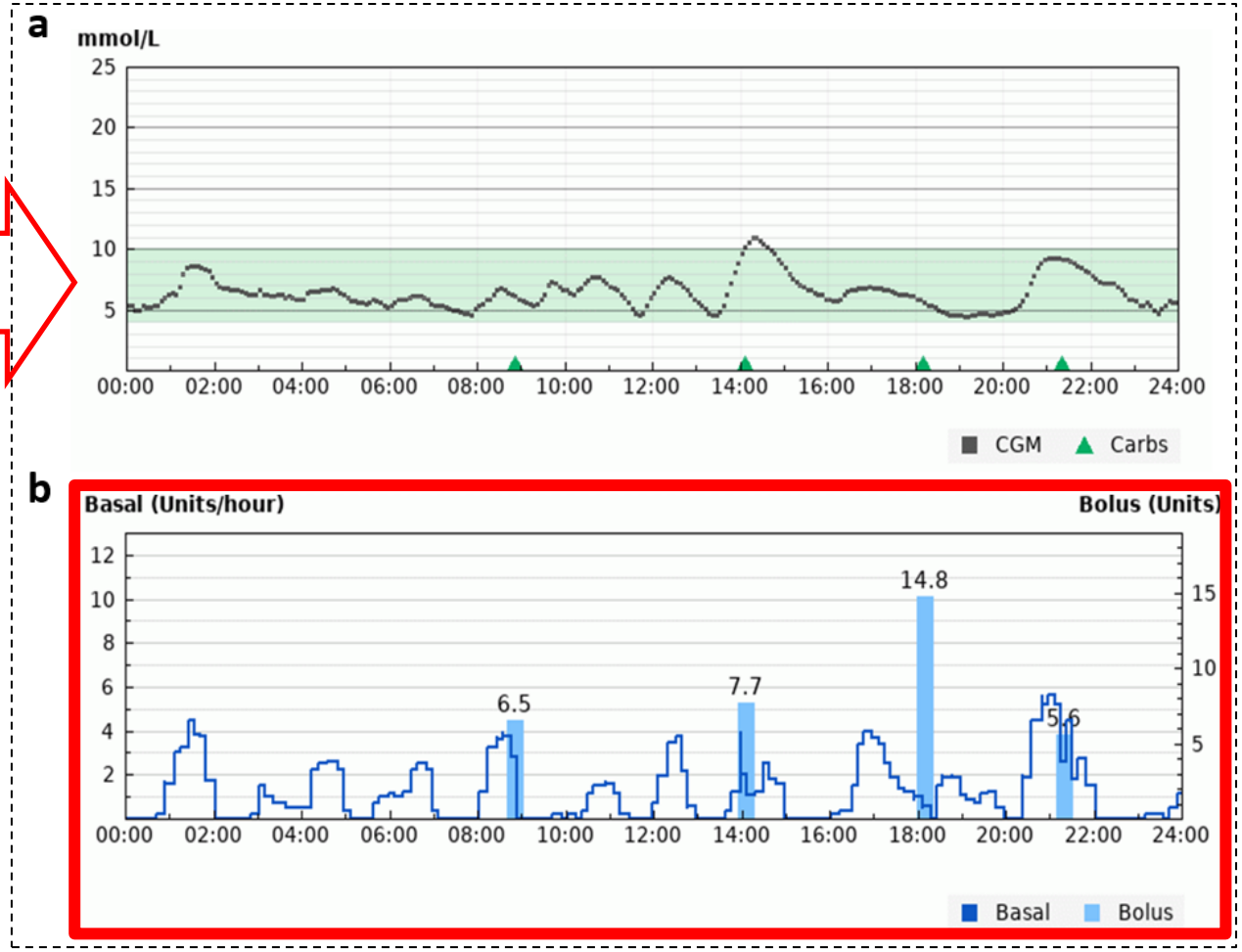


Boughton and Hovorka (2021) Diabetologia DOI 10.1007/s00125-021-05391-w

Continuous glucose monitoring (CGM)

Hybrid closed-loop glucose control:
(a) 24 h of sensor glucose data.
(b) Algorithm-driven insulin delivery and manual insulin boluses.





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Scientific Paradigm Shifts of Diabetes Mellitus

- Major advances in the mechanistic understanding of diabetes and its complications have been achieved.
- Disease-modifying molecular-target guided therapeutics are now available.
- In appropriately selected patients, inducing diabetes remission (dietary, pharmacological and surgical options) may be the preferred treatment strategies.
- Monogenic diabetes is the “poster-boy” for precision diabetes medicine.
- Technological advances in glucose monitoring and insulin delivery have made intensive diabetes management a realizable goal.

The future of war against diabetes is now

Acknowledgement

- Diabetes Centre
- Endocrinology Dept
- CRU Research Team
- Collaborators
  - Dr Kon Y C Winston (TTSH)
  - Dr Fabian Yap KP (KKH)
  - Dr Rashida Farhad Vasanwala (KKH)
  - Dr Joan Khoo (CGH)
  - Dr Loh Wann Jia (CGH)
  - Dr Lim Ziliang (NHGP-Yishun)
  - Dr Mogilan Mohan (NHGP-Yishun)
  - Dr Kung Jian Ming (NHGP-Yishun)

Khoo Teck Puat Hospital, National Healthcare Group

Admiralty Medical Centre, National Healthcare Group

Tan Tock Seng Hospital, National Healthcare Group

National Healthcare Group Polyclinics

KK Women's and Children's Hospital, SingHealth

Changi General Hospital, SingHealth

NMRC National Medical Research Council Singapore

THANK YOU

FOR YOUR

SUPPORT!

Alexandra Health Funds