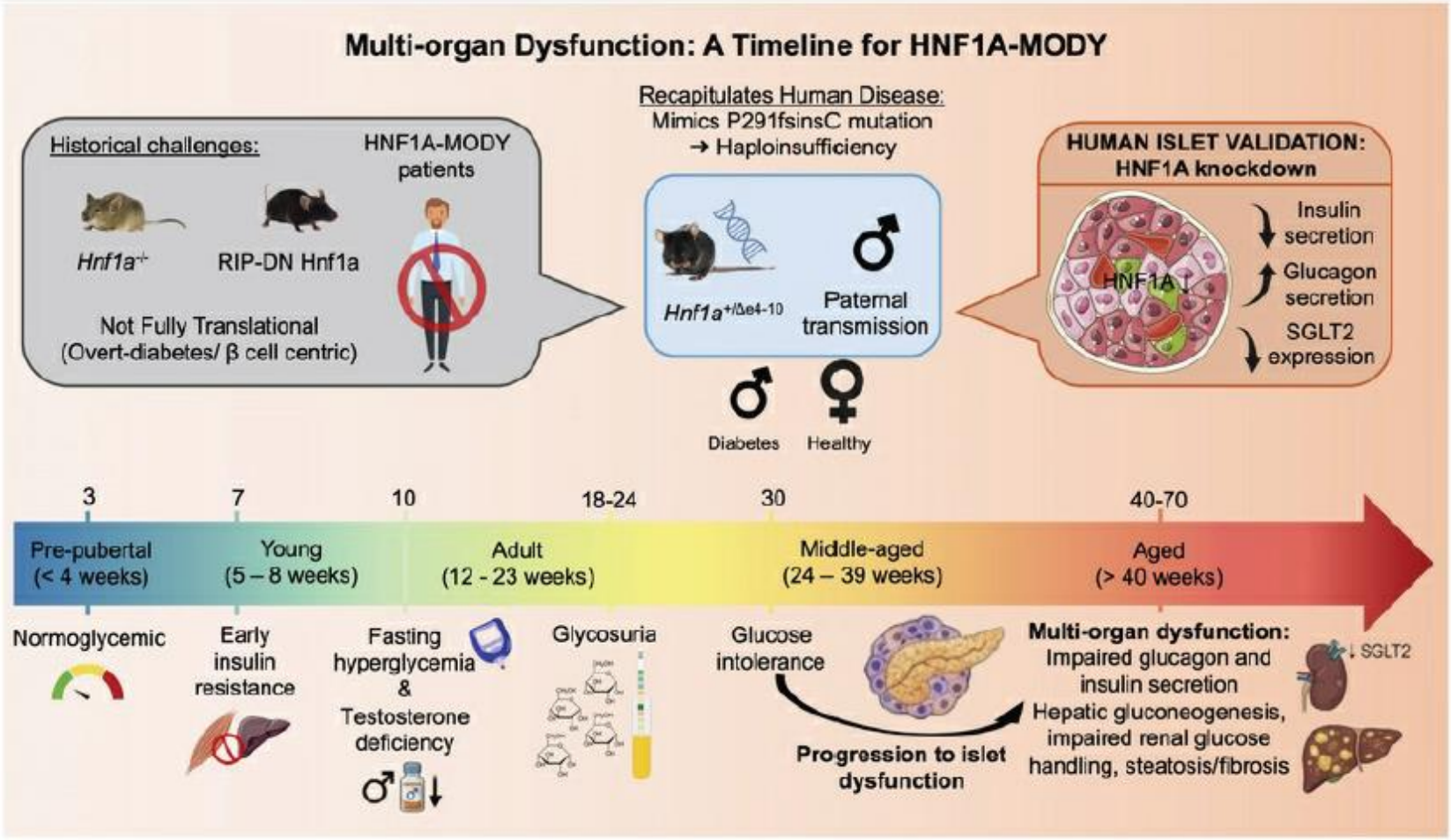
Interhospital Endocrine Conference

A 36-year-old non-obese Thai male with a history of T2D with worsening glycemic control

HNF1A-MODY

- HNF1A is a human gene on chromosome 12 (12q24.31) encoding the hepatocyte nuclear factor 1-alpha (HNF-1α) transcription factor.
- It regulates liver development, beta-cell function in the pancreas, and gene expression in the kidneys and intestines.



Li L-M, et al. *Front Endocrinol (Lausanne). 2022;13:829565.*

Louvet I, et al. *JCI Insight*. 2026;11(9):e198095.

Table 1 The causative genes for maturity-onset diabetes of the young (MODY) and medical conditions associated with each MODY subtype

MODY gene	Frequency (% in MODYs)	Pathophysiology	Other features	Possible treatment
HNF4α	5	β-Cell dysfunction	Neonatal diabetes, hyperinsulinemic hypoglycemia during infancy, low triglycerides	Sensitive to sulfonylurea
GCK	15–20	Glucose sensing defect	Stable mild fasting glucose	No medication, or Diet
HNF1α	30–50	β-Cell dysfunction	Glucosuria	Sensitive to sulfonylurea
PDX1	<1	β-Cell dysfunction	Homozygote: permanent neonatal diabetes, pancreas agenesis	Diet or OAD or insulin
HNF1β	5	β-Cell dysfunction	Renal malformations, genito-urinary tract anomalies, pancreatic hypoplasia, low birth weight	Insulin
NEUROD1	<1	β-Cell dysfunction	Neonatal diabetes, child or adult-onset diabetes neurological abnormalities.	OAD or insulin
KLF11	<1	β-Cell dysfunction	Similar to type 2 diabetes	OAD or insulin
CEL	<1	Pancreas endocrine and exocrine dysfunction	Exocrine dysfunction, lipomatosis	OAD or insulin
PAX4	<1	β-Cell dysfunction	Ketoacidosis-prone	Diet or OAD or insulin
INS	<1	Insulin gene mutation	Neonatal diabetes, child or adult-onset diabetes	OAD or insulin
BLK	<1	Insulin secretion defect	Overweight, relative insulin secretion failure	Diet or OAD or insulin
ABCC8	<1	ATP-sensitive potassium channel dysfunction	Homozygote: permanent neonatal diabetes, Heterozygote: transient neonatal diabetes	OAD (sulfonylurea)
KCNJ11	<1	ATP-sensitive potassium channel dysfunction	Homozygote: neonatal diabetes	OAD or insulin
APPL1	<1	Insulin secretion defect	Child or adult-onset diabetes	Diet or OAD or insulin

Urakami T. *Diabetes Metab Syndr Obes*. 2019;12:1047-1056.

Common Types of MODY and Their Clinical Clues

Subtype	Key clues
GCK-MODY	Mild stable fasting hyperglycemia
HNF1A-MODY	Progressive diabetes, glycosuria, sulfonylurea sensitive
HNF4A-MODY	Neonatal macrosomia/hyperinsulinism history
HNF1B-MODY	Renal abnormalities, hypomagnesemia

Distinguish MODY From Type 2 Diabetes

- MODY calculator : Traditional EXETER, Modified EXETER, Chinese calculator, Indian calculator

American Diabetes Association. Diabetes Care

LETTER ▸ Diabetes Care. 2024 Nov 18;48(1):e3–e5. doi: 10.2337/dc24-1565

MODY Calculator and Clinical Features Routinely Used to Distinguish MODY From Type 2 Diabetes in Adults Perform Poorly for Youth Clinically Diagnosed With Type 2 Diabetes

Raymond J Kreienkamp [1,2,3,4], Beverley M Shields [5], Toni I Pollin [6], Amy S Shah [7], Angela D Liese [8], Anna Bellatorre [9], Catherine Pihoker [10], Mustafa Tosur [11,12], Jose C Florez [2,3,4], Shylaja Srinivasan [13], Andrew T Hattersley [5], Miriam S Udler [2,3,4], Maria J Redondo [11]

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC11664197 PMID: 39556464

Diabetologia (2012) 55:1265–1272
DOI 10.1007/s00125-011-2418-8

ARTICLE

The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes

B. M. Shields · T. J. McDonald · S. Ellard · M. J. Campbell · C. Hyde · A. T. Hattersley

Journal of Diabetes Science and Technology

Impact Factor: 4.9 / 5-Year Impact Factor: 4.7 | Journal Homepage | Submission Guidelines

Restricted access | Research article | First published online March 23, 2026 | Request permissions

Development of a Calculator for *HNF1A*- and *HNF4A*-*MODY* in Asian Indians

Viswanathan Mohan, MD, DSc, Ulagamadesan Venkatesan, PhD, [...], and Ranjit Unnikrishnan, MD (+5) View all authors and affiliations

Volume 20, Issue 3 | https://doi.org/10.1177/19322968261429944 | View article versions

เทพรารินทร์ ศูนย์เบาหวาน ไทรอยด์ และต่อมไร้ท่อ Service Education Research

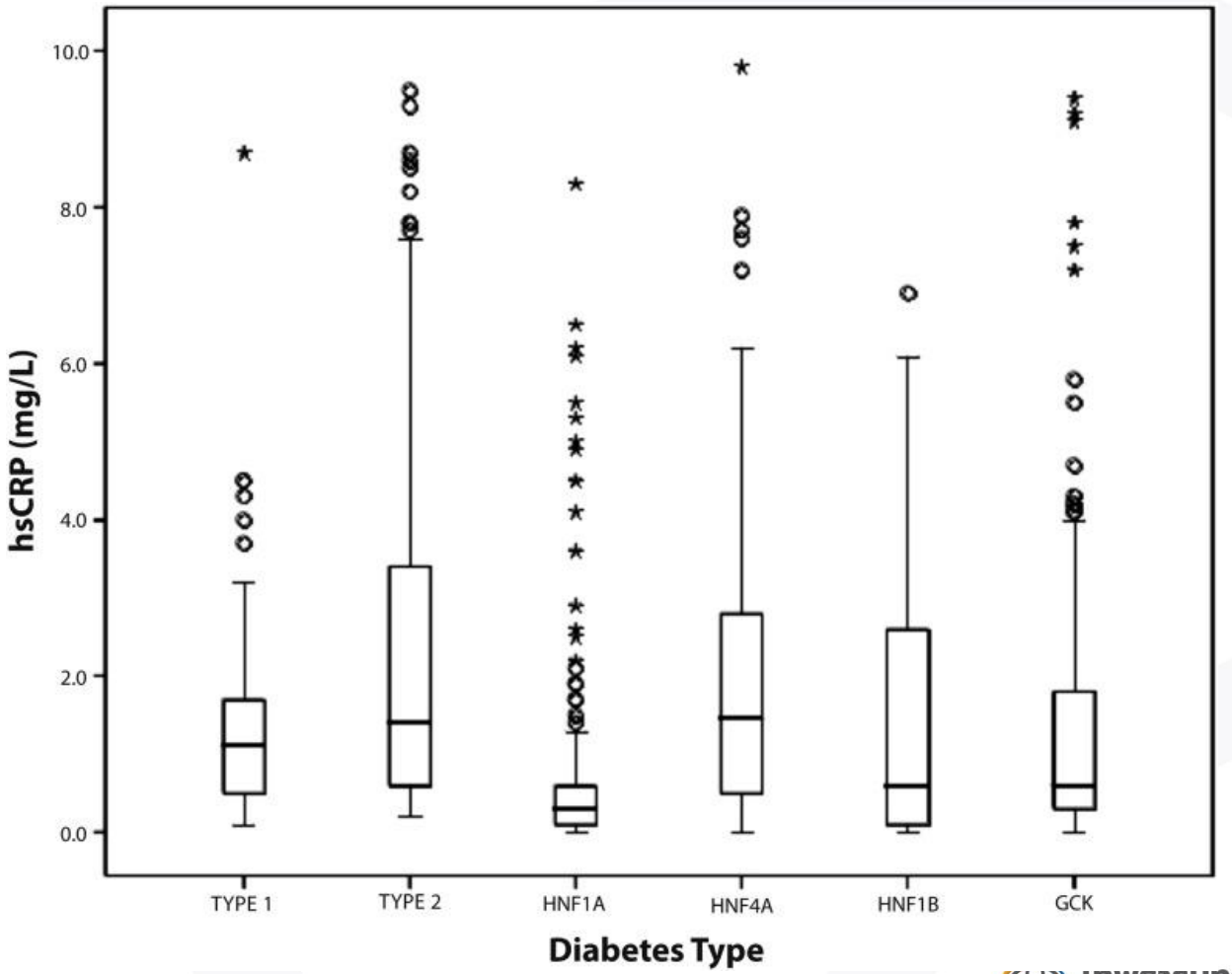
Distinguish MODY From Type 2 Diabetes

Calculator	Populations	Study type	Variables	Pros	Cons
Traditional Exeter (2012)	White European UK	GCK, HNF1A, HNF4A	Age at diagnosis, BMI, HbA1c, treatment, family history	• No C-peptide/ Antibodies value need • Well validated • AUC 0.95	• Decrease performance in Chinese, Indian, Brazilian
Modified Exeter	Adaptation/validation ใน populations อื่น	MODY vs T1D/T2D	Exeter concept + C-peptide lipid profile ethnicity-specific parameters	• Better sensitivity	• Not ethnicity-specific
Chinese Calculator	Chinese young-onset non-T1D	GCK, HNF1A, HNF4A, HNF1B	current age, age at diagnosis, sex, BMI, systolic BP, HDL-C, LDL-C, triglyceride, fasting C-peptide	• Suitable in Chinese	• No external validation
Indian Calculator	Asian Indian	HNF1A/HNF4A	Age at diagnosis, BMI, parental history, HbA1c ± HDL ± stimulated C-peptide	• Developed from large Indian cohort	• New • Focus only HNF1A/HNF4A

AUC: Area Under the Curve

hsCRP in *HNF1A*-MODY

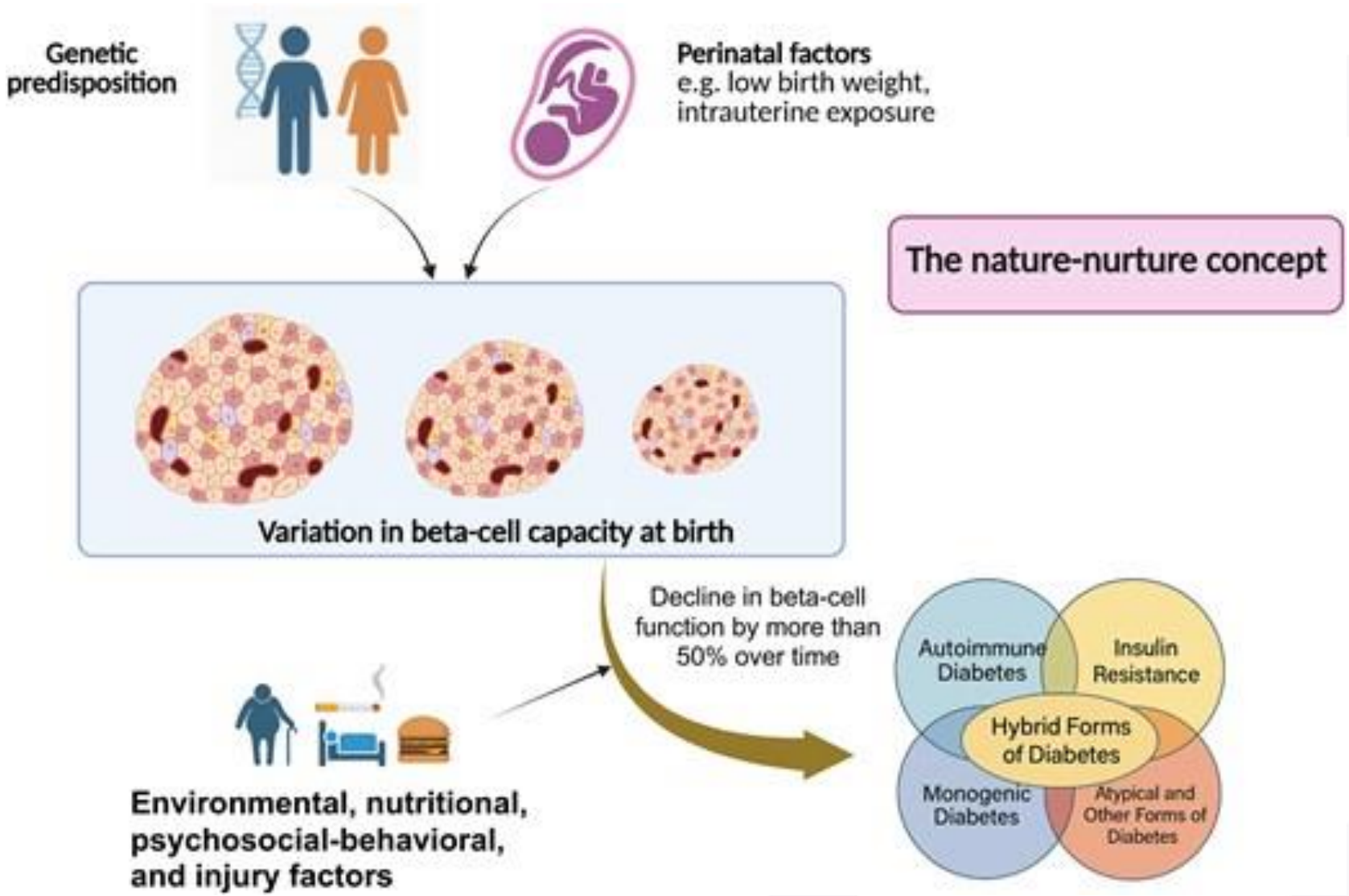
- Use as a screening for MODY
- **Low hsCRP** is a biomarker of reduced *HNF1A* transcriptional activity.
- No universal cut-off point (but mostly use <0.2-0.5 mg/L)



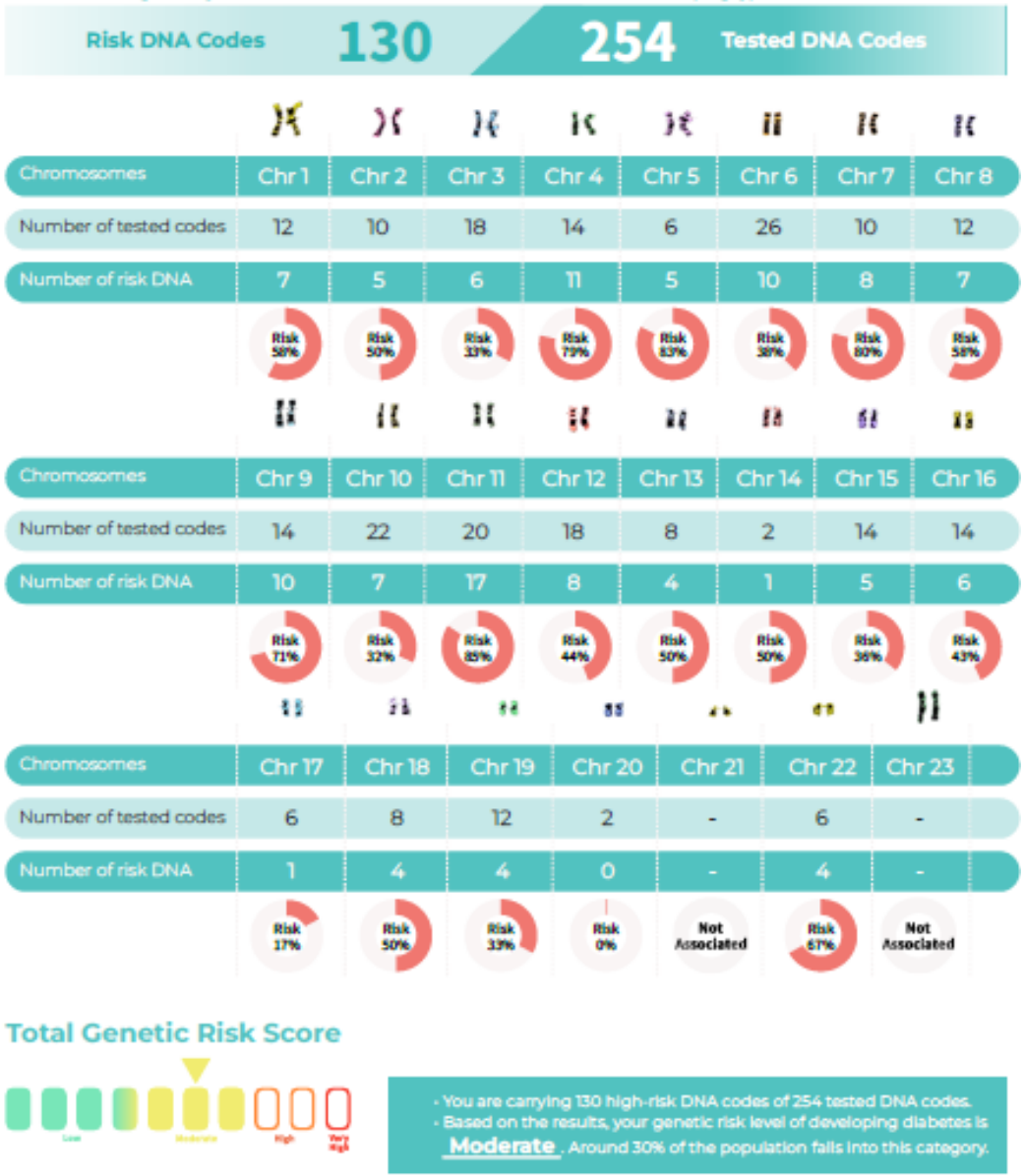
hsCRP: high-sensitivity C-reactive protein

McDonald Tjet al. *Diabetes Care*. 2011;34(8):1860-1862.

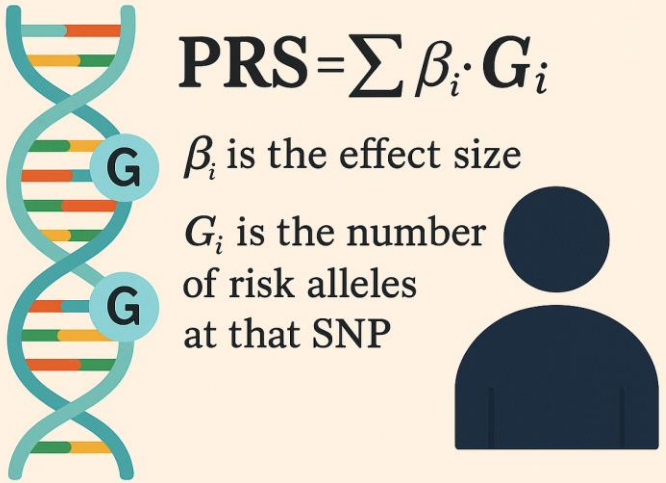
The nature-nurture concept



Polygenic risk score



- Polygenic Risk Score (PRS): a quantitative measure that combines the effects of numerous genetic variants across the genome to estimate an individual's genetic susceptibility to a specific disease.



$$PRS = \sum \beta_i \cdot G_i$$

β_i is the effect size

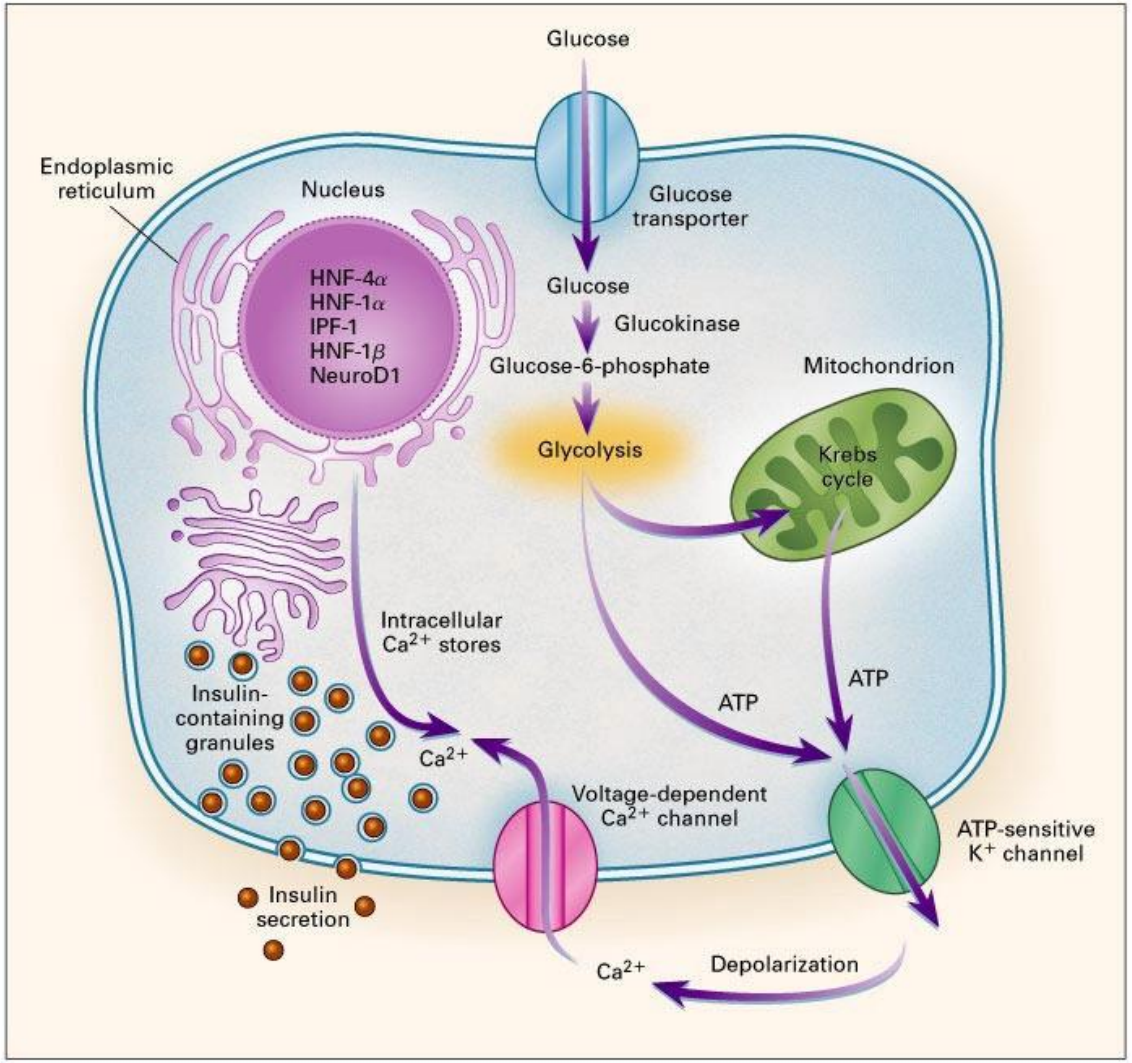
G_i is the number of risk alleles at that SNP

MODY = one gene, large effect

T2D = many genes, small effects

Chen SF,et al. Genome Med. 2020 Nov 23;12(1):100.

Sulfonylurea in *HNF1A*-MODY



- Insulin sensitivity is typically preserved.
- Endogenous insulin secretion remains present.
- Sulfonylureas effectively close KATP channels, thereby stimulating insulin secretion.

excellent response to very low dose sulfonylurea

Fajans SS, et al. *N Engl J Med*. 2001;345(13):971-980.

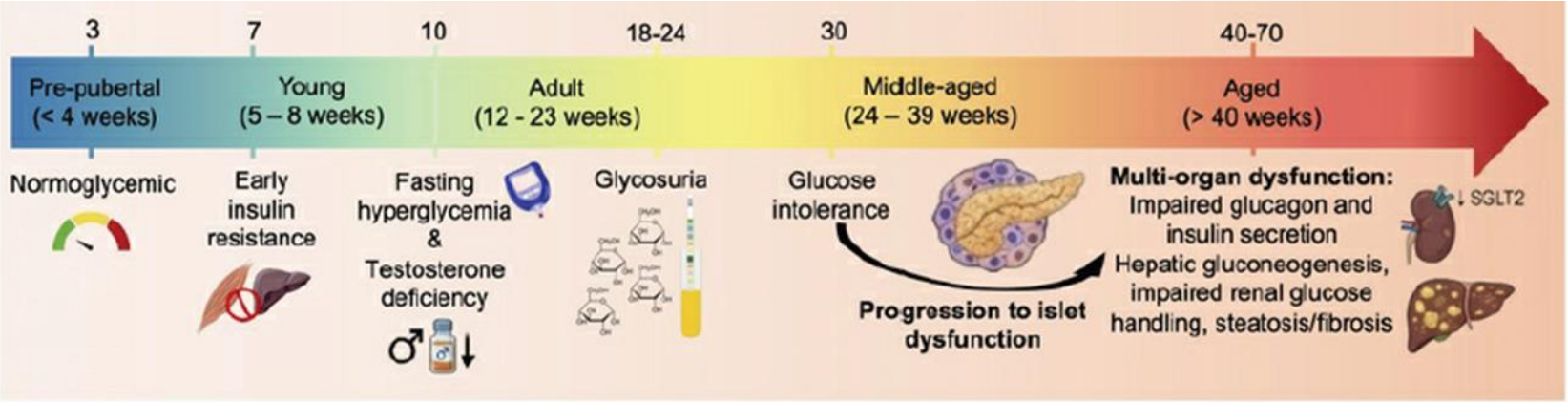
First-line therapy: Low-dose sulfonylurea (SU)

- First-line treatment for most patients with *HNF1A*-MODY.
- Patients exhibit marked **sulfonylurea sensitivity**, often achieving excellent glycemic control with doses substantially lower than those used in type 2 diabetes.
- Initiate at a **low dose** and titrate gradually based on glycemic response.
- If the patient is already receiving insulin, insulin doses should be reduced or discontinued when SU is started to minimize hypoglycemia.

Broome DT, et. *J Clin Endocrinol Metab*. 2021;106(1):237-250.

HNF1A-MODY

- **Progressive decline in β-cell function**
- Despite excellent initial response, glycemic control often deteriorates over time.
- Secondary treatment failure may occur after approximately 3–25 years, depending on age at diagnosis and residual β-cell function.
- Additional therapies are frequently required later in the disease course.



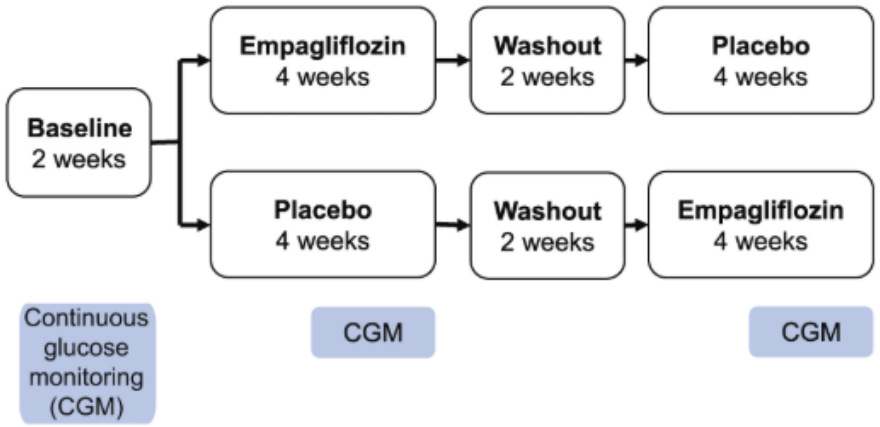
Fajans SS, Bell GI. *Diabetes Care*. 2011;34(8):1878-1884.
Louvet I, et al. *JCI Insight*. 2026;11(9):e198095.

Empagliflozin in *HNF1A*-MODY

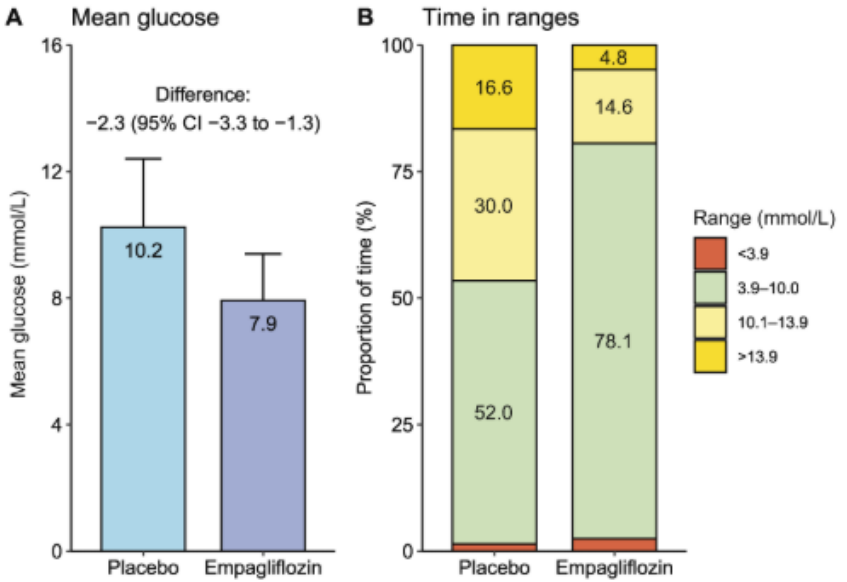
Empagliflozin in HNF1A-MODY (MODY3)—a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

Aim: Assess the glucose-lowering effect of the sodium-glucose cotransporter 2 inhibitor empagliflozin in individuals with HNF1A maturity-onset diabetes of the young (HNF1A-MODY)

Study outline



Results



In individuals with HNF1A-MODY, empagliflozin improves glycemia.

Maagensen H, Høyerup SO, Jensen JS, et al. *Diabetes Care*. Published online January 12, 2026.

SGLT2 inhibitors: Use with caution

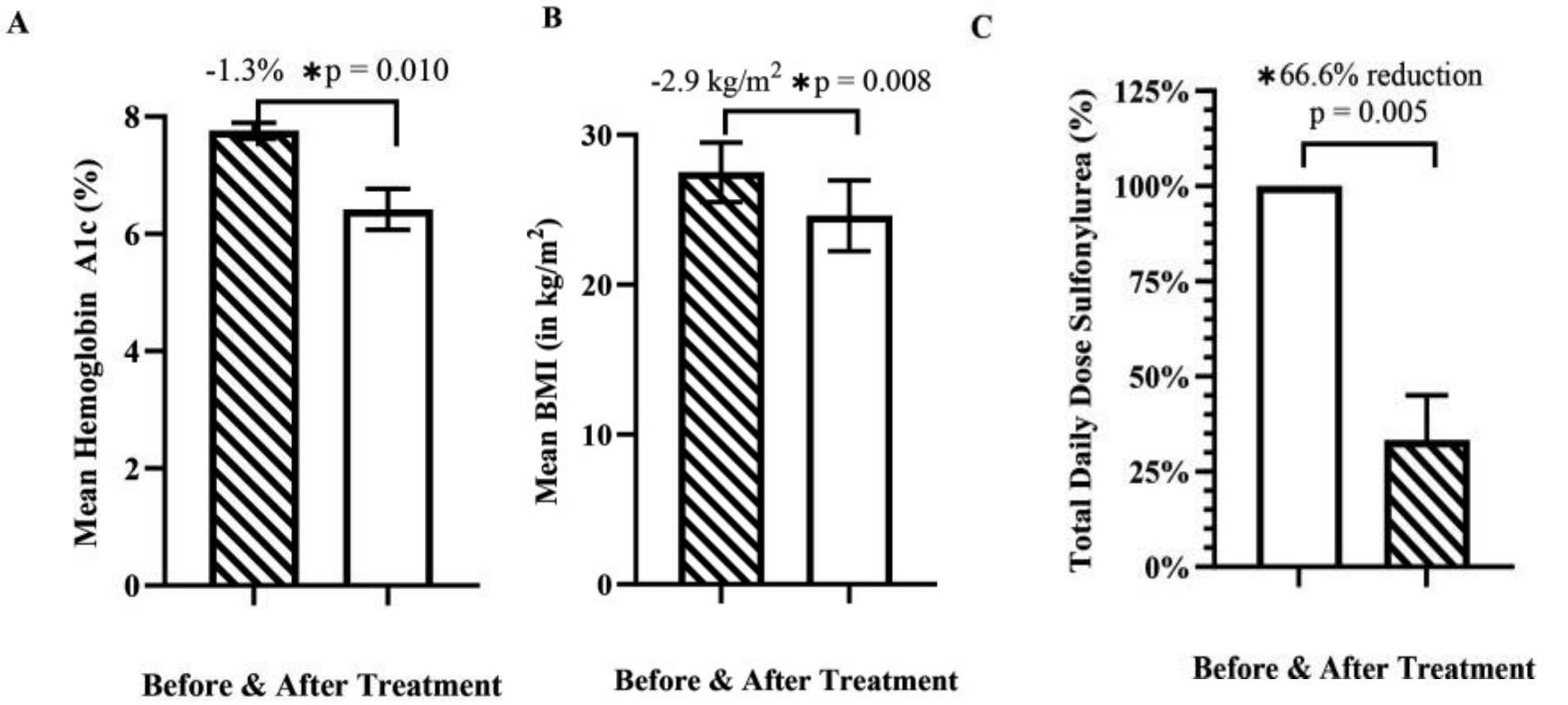
- HNF1A regulates SGLT2 expression in the kidney.
- Patients with HNF1A-MODY already have reduced SGLT2 expression and increased glycosuria.

Potential concerns

- Excessive glycosuria
- Volume depletion and dehydration
- Genital infections
- Diabetic ketoacidosis (DKA)

Broome DT, et. *J Clin Endocrinol Metab*. 2021;106(1):237-250.

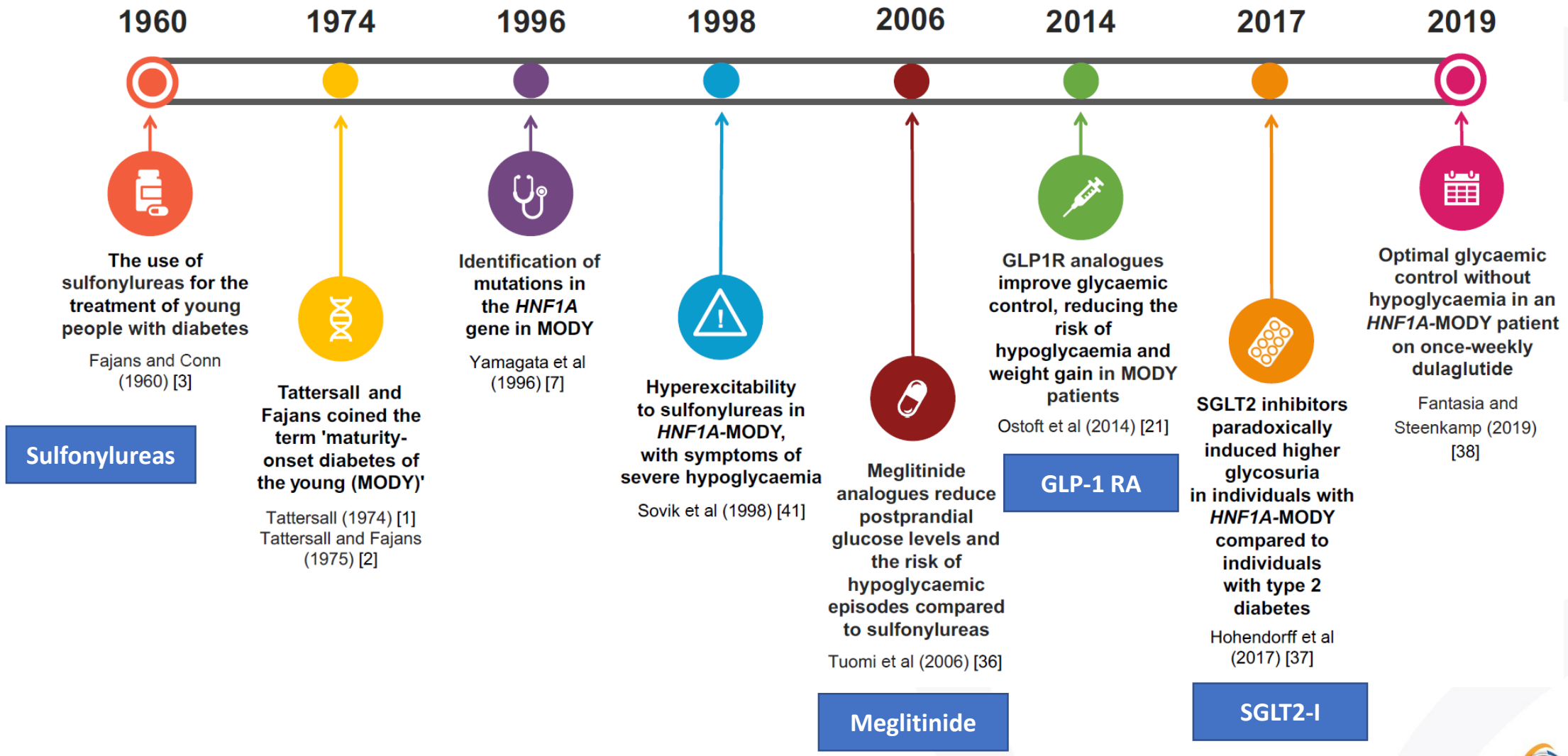
GLP-1 RA in *HNF1A*-MODY



- GLP-1 RA and dual GIP/GLP-1 RA are potential effective treatments for *HNF1A*-MODY, *HNF4A*-MODY, *ABCC8*-MODY, and *HNF1B*-MODY.

Mehdi AZ, et al. *BMJ Open Diabetes Res Care*. 2025;13(2):e004885.

Timeline of *HNF1A* mutation discovery and pharmacological strategies for the treatment of *HNF1A*-MODY



Bonner C, Saponaro C. *Diabetologia*. 2022;65(11):1825-1829.

Practical points

1. *HNF1A*-MODY ≠ lifelong sulfonylurea monotherapy
2. An excellent response to sulfonylureas is a well-recognized **phenotypic clue** for *HNF1A*-MODY, but it is **not a diagnostic criterion**.
3. When glycemic control deteriorates, there is no need to switch immediately to insulin. Depending on the individual patient's circumstances, treatment options may include DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2i, Insulin
4. Age at diagnosis and disease duration are critically important.