LABORATOIRE DE RECHERCHE SUR LE DIABETE
UNIVERSITE ABOUBEKR BELKAID
FACULTE DE MEDECINE BENAOUDA BENZERDJEB
CHU TIDJANI DAMERDJI

Médecine de précision dans le diabète
(Precision medicine in diabetes)

Ali Lounici

1er Séminaire du laboratoire de Recherche sur le Diabète

7émes Journée AMIWIT

Vendredi 29 & Samedi 30 Novembre 2019

Faculté SNVTU - Université de Tlemcen -

DEFINITION

- **What is precision medicine:**

- La médecine de précision consiste à adapter le traitement médical aux caractéristiques individuelles de chaque patient ou sous-population.

- **What is precision medicine in diabetes:**

- L'utilisation d'une profonde compréhension de la maladie, des mécanismes et des biomarqueurs, mais aussi de l'engagement des patients et des cliniciens et de l'utilisation de ces biomarqueurs et de ces connaissances génétiques pour mettre au point les meilleurs traitements individuels permettant d'obtenir les meilleurs résultats.

Precision Medicine in Diabetes

"an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"

A Global Overview of Precision Medicine in Type 2 Diabetes

Hugo Fitipaldi,[1] Mark I. McCarthy,[2,3] Jose C. Florez,[4,5,6] and Paul W. Franks[1,2,7,8]

Diabetes 2018;67:1911–1922 | https://doi.org/10.2337/dbi17-0045

Review Article

Future Roadmaps for Precision Medicine Applied to Diabetes: Rising to the Challenge of Heterogeneity

P. Bowman,[1,2] S. E. Flanagan,[1] and A. T. Hattersley[1,2]

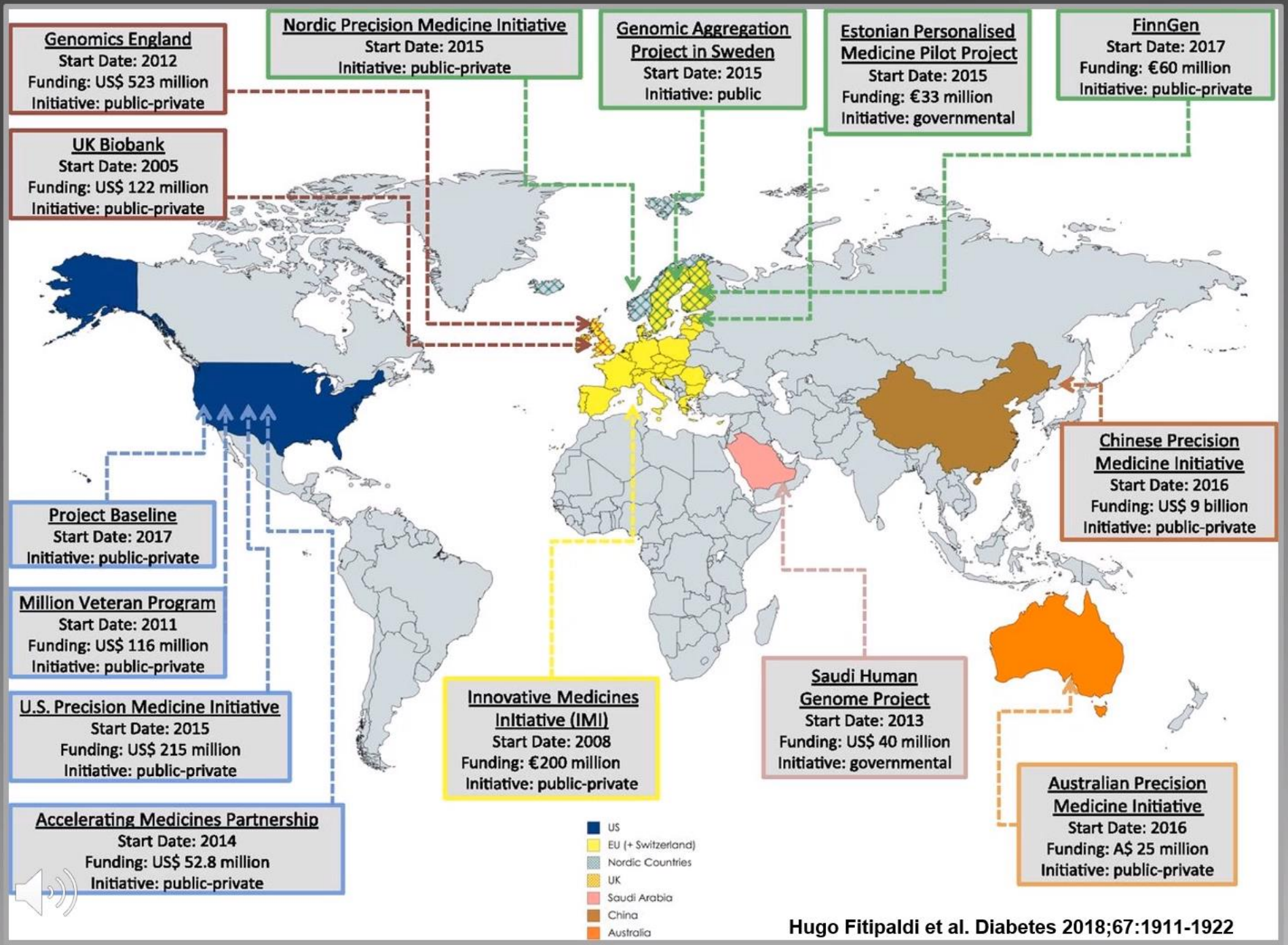
[1]*University of Exeter Medical School, Exeter, UK*
[2]*Exeter NIHR Clinical Research Facility, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK*

"specific treatments can be targeted to groups of individuals with specific genetic, cellular, or molecular features"

Journal of Diabetes Research
Vol.2018, Article ID 3061620 12pages
http://doi.org/10.115/2018/3061620

American Diabetes Association.

Precision Medicine Initiatives
Are happening globally



Hugo Fitipaldi et al. Diabetes 2018;67:1911-1922

Precision Medicine Initiatives are Happening Globally

Also: India, Nigeria

American Diabetes Association.

What are approaches to Precision Medicine in Diabetes?

- Animal models have important limitations in translation to human type 1 and type 2 diabetes
- Human research is needed to address the best approaches to precision medicine
- Precision medicine must be based on sharing large data sets and electronic medical records
- New islet and other organ specific data must inform new approaches
- Precision medicine must take into account cost-effectiveness, quality of life, and patient acceptance
- monogenic diabetes is the best example of precision medicine in diabetes that is specific, and cost-effective

Roadmap For Human Diabetes Research

Human islets/beta cells ⟷ Human populations

Science:

Omics, biomarkers, epidemiology, behavioral health

Clinical Translation

Targeted treatments

Cost Effectiveness

Quality of Life

Human-specific research methods can be applied to key areas relevant to diabetes pathophysiology, leading to development of new targeted treatments.

(Bowman et al 2018)

Precision Medicine in Diabetes:

Correct diagnosis, informed treatment, road to prevention

Journal of Diabetes Research
Volume 2018, Article ID 3061620, 12 pages
https://doi.org/10.1155/2018/3061620

American Diabetes Association.

Precision Medicine:

Lessons from Oncology

- RNA-Seq tumor and genomics profiling for mutations in kinases and other targets
- In vitro testing of tumor derived organoids
- Proteomic approaches to tumor markers
- High throughput applications of drugs for screening against patient derived cells
- Genetic/epigenetic alterations and drug responses
- Cell changes during disease progression
- drug resistance / microbiome/ Deep learning
- cost effectiveness / quality of life and patient preferences /behavioral health

American Diabetes Association.

What can we learn from monogenic diabetes to advance precision medicine?

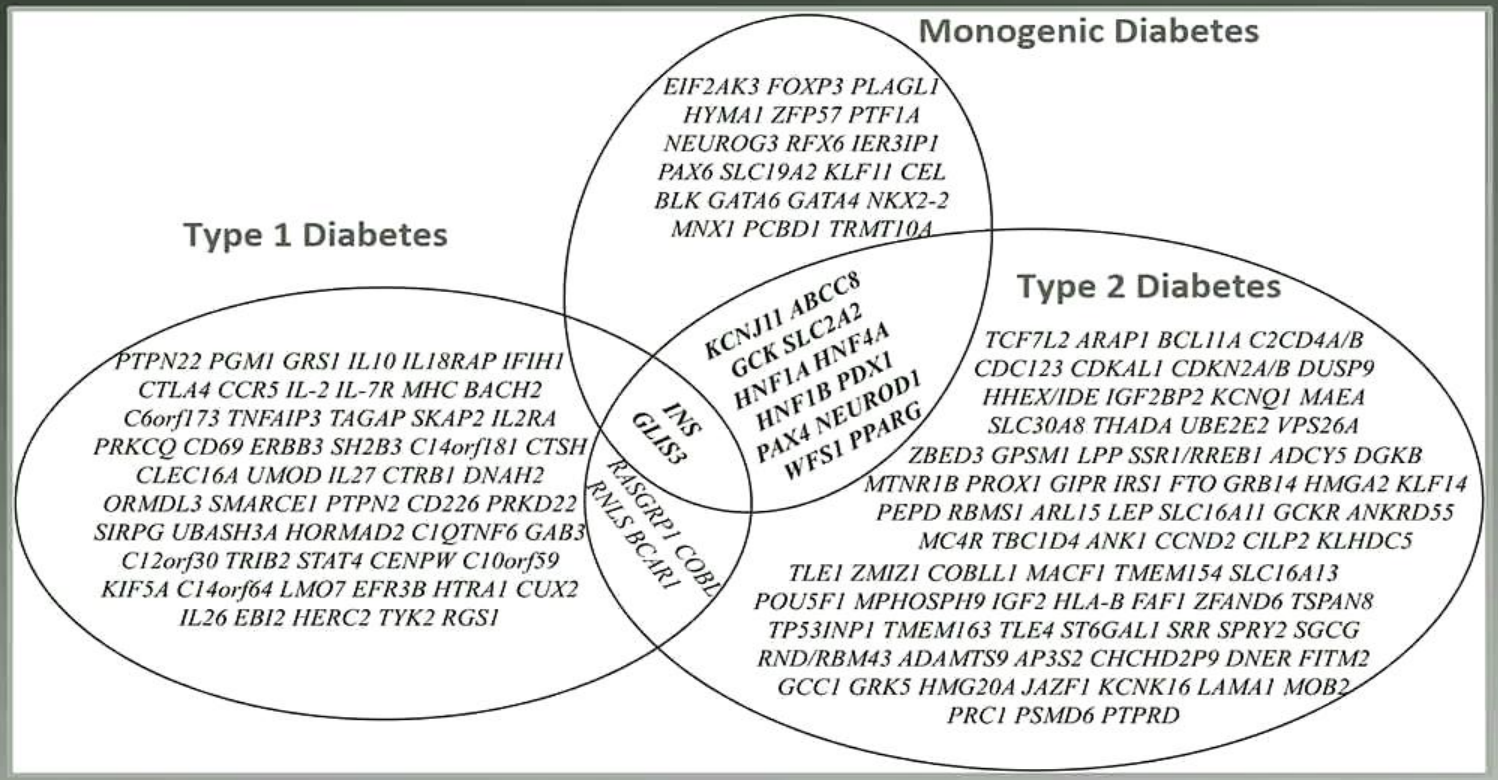
importance of basic research

careful attention to diagnostics and phenotyping

relationship between monogenic and polygenic conditions

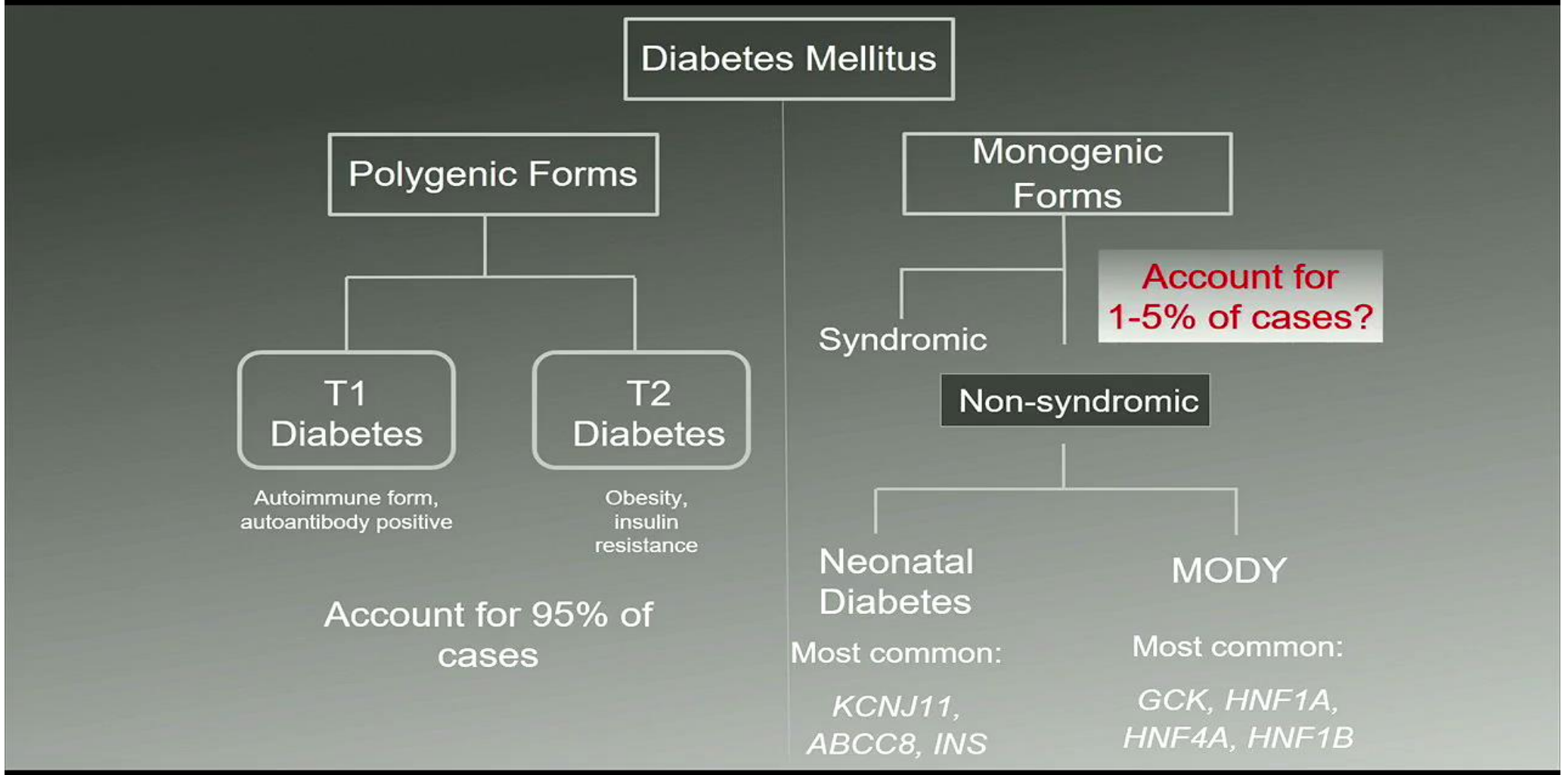
American Diabetes Association.

Monogenic Diabetes: What It Teaches Us about the Common Forms of Diabetes



Polymorphisms in genes involved in monogenic forms of diabetes also play a role in polygenic T2D

Yang Y, Chan L. Monogenic Diabetes: What It Teaches Us on the Common Forms of Type 1 and Type 2 Diabetes. Endocr Rev. 2016 Jun;37(3):190-222.


Diabetes Mellitus
Polygenic Forms
Monogenic Forms
T1 Diabetes
T2 Diabetes
Autoimmune form, autoantibody positive
Obesity, insulin resistance
Account for 95% of cases
Account for 1-5% of cases?
Syndromic
Non-syndromic
Neonatal Diabetes
Most common:
KCNJ11, ABCC8, INS
MODY
Most common:
GCK, HNF1A, HNF4A, HNF1B

Monogenic Forms of Diabetes

Understand the phenotype-genotype connection

Take a careful family history

Identify those who should have cost-effective genetic testing

Decide how those genes should be evaluated

Realize that not all phenotypes will have a known genetic cause

Recognize that therapy may be directed by the specific mutation

Act on the implications for the other family members

American Diabetes Association.

Precision medicine in type 2 diabetes: Approche alternative pratique

Approche alternative pratique for precision medicine in type 2 diabetes

- Diagnostiquer les formes monogeniques du diabete
- Approche du typage du diabete en clusters au diagnostic
- Approche de l'individuation de l'objectif glycémique
- Identification des caractéristiques phénotypiques cliniques ou des biomarqueurs solidement associés avec une réponse d'une molécule donnée. (Variation de la réponse individuelle aux différents traitements dans le diabète)
- Safety : CV+++ (Glitazones, I-DPP4, Sulfamides ?) Rein, Os (Glitazones, Gliflozines), Foie, Cerveau (Cognitive), Cancer (Hautes doses insuline ?)

Diagnostiquer les formes monogeniques du diabète

Standards of Medical Care in Diabetes – 2019

Monogenic Diabetes

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, nonobese, lacking other metabolic features especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100-150 mg/dL), stable A1C between 5.6 and 7.6%, especially if non obese.
- Children and adults, diagnosed in early adulthood, who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. **A**
- Consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Maturity-Onset Diabetes of the Young (MODY)

- A heterogeneous metabolic disorder due to heterozygous monogenic mutations
- Accounts for 1-2% of all cases of diabetes.
- Onset of diabetes early in life: childhood, adolescence, young adulthood (but may be discovered at any age).
- Autosomal dominant inheritance (usually)
- Non obese (usually)
- May simply be classified as having T2D: non-ketotic and/or non-acute presentation, but occurring usually before the age of 25 years.
- No islet autoimmunity (usually)
- Can be misdiagnosed as T1D: rapid failure with oral drugs and/or young onset of presentation.
- Primarily due to gene defects in insulin secretion (usually)
- Up to now, there are at least 14 genetic subtypes of MODY each with distinct clinical characteristics and responsible genes.

Table 1 A summary of genetic mutations associated with maturity onset diabetes of the young (MODY)

Subtype	Gene	Location	Etiology	Features
MODY 1(82)	HNF-4α	20q13.12	Insulin secretion defect	Progressive hyperglycemia
MODY 2(75)	Glucokinase	7p13	glucose sensing and Insulin secretion defect	Early onset; mild hyperglycemia, minor microvascular disease
MODY 3(83)	HNF-1α	12q24.31	Insulin secretion defect	Progressive hyperglycemia, sensitive to SU
MODY 4(84)	PDX1/IPF1	13q12.2	Insulin secretion defect	Early onset.
MODY 5(85)	HNF-1β	17q12	Insulin secretion defect	Variable age at onset, range infancy to adult; progressive
MODY 6(86)	NeuroD1	2q31.3	Insulin secretion defect	Early onset.
MODY 7(87)	KLF11	2p25.1	Insulin secretion defect	Very rare
MODY 8(88)	CEL	9q34.13	beta-cell defect	Endocrine and exocrine pancreatic insufficiency
MODY 9(89)	PAX4	7q32.1	Little data	Very rare
MODY 10(90)	INS	11p15.5	Insulin secretion defect	Diagnosed at 20s to 30s. Can cause neonatal diabetes, antibody
MODY 11(91)	BLK	8p23.1	Defect in insulin synthesis and secretion	Onset often before age 25. Some patients require insulin for
MODY 12(92)	ABCC8	11p15.1	Little data	Frequent cause of neonatal diabetes but can rarely cause MODY
MODY 13(93)	KCNJ11	11p15.1	Insulin secretion defect	Sulfonylurea therapy effective
MODY 14(94)	APPL1	3p14.3	Defect in insulin signaling pathway	With elevated FBG and HbA1C and onset between 30s and 50s.

Maturity-Onset Diabetes of the Young (MODY)

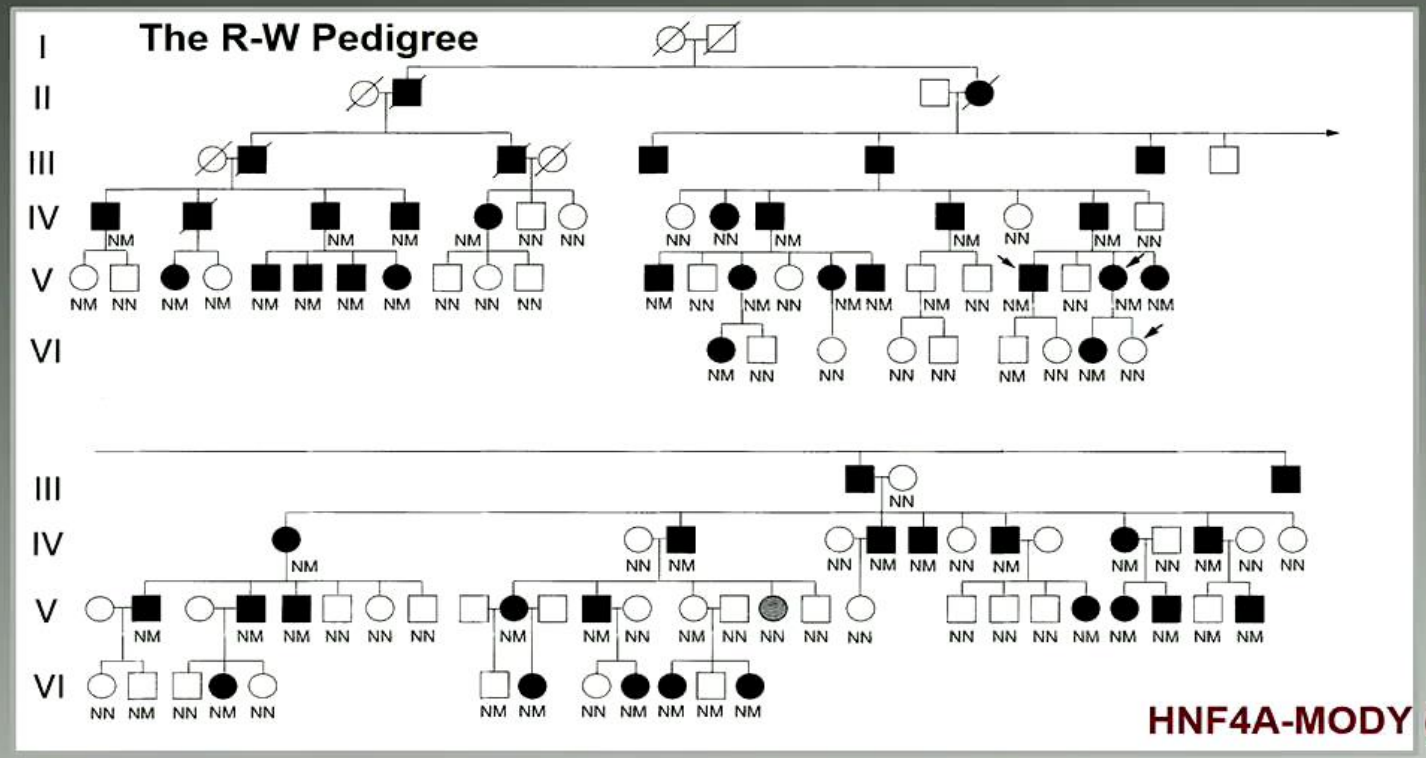
	GENE MUTATION	CLINICAL FEATURES
MODY 1	Hepatocyte nuclear factor **(HNF-4 α)** gene	Progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
MODY 2	Glucokinase (**GCK**) gene:	Stable, non progressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (0.54 mg/dL)
MODY 3	Hepatocyte nuclear factor **(HNF1 α)** gene	Progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (0.90 mg/dL); sensitive to sulfonylureas

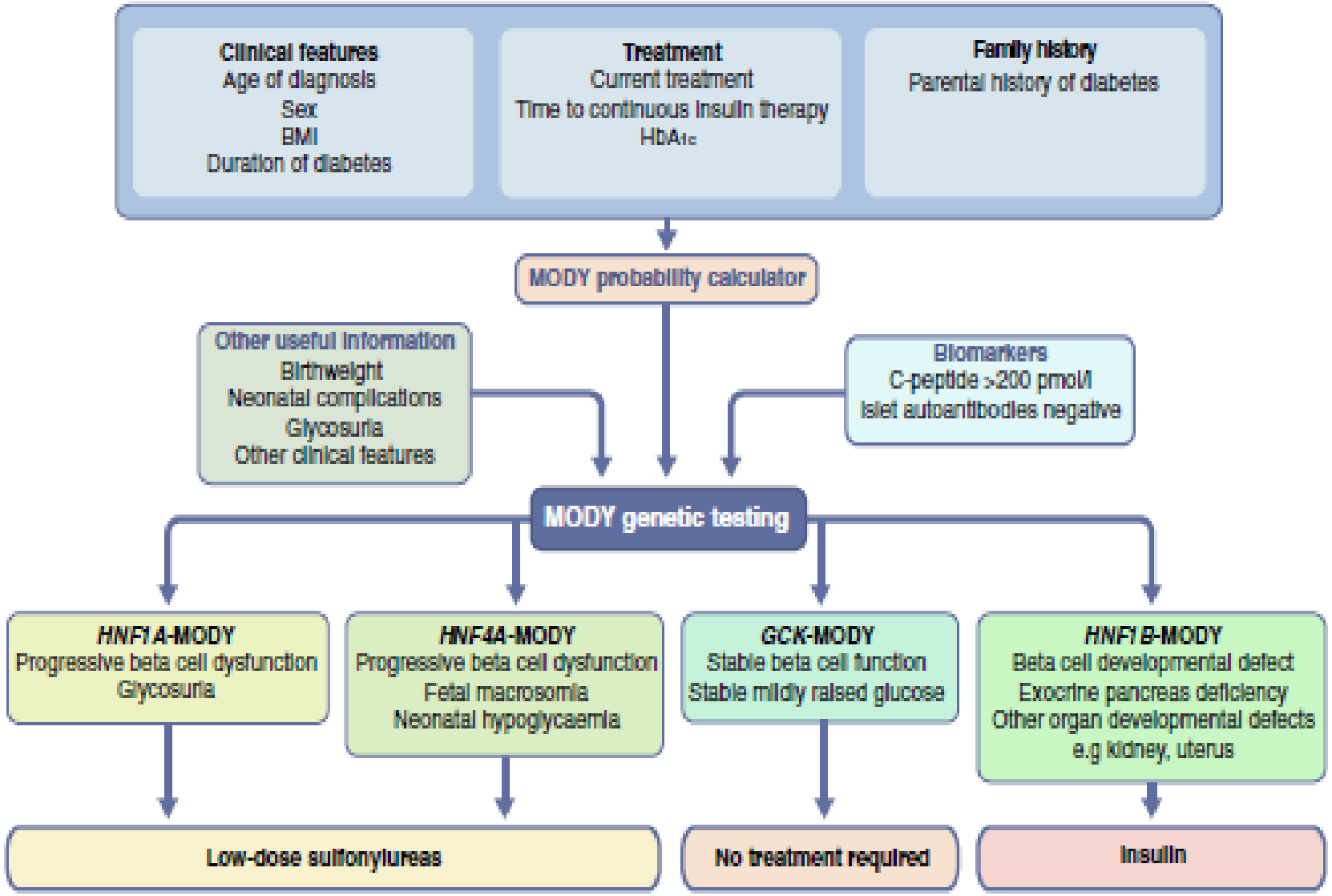
University of Chicago and University of Michigan Pioneered the Genetic Studies of Diabetes

Stefan S. Fajans

University of Michigan

1918-2014




Clinical features
Age of diagnosis
Sex
BMI
Duration of diabetes
Treatment
Current treatment
Time to continuous insulin therapy
HbA1c
Family history
Parental history of diabetes
MODY probability calculator
Other useful information
Birthweight
Neonatal complications
Glycosuria
Other clinical features
Biomarkers
C-peptide >200 pmol/l
Islet autoantibodies negative
MODY genetic testing
HNF1A-MODY
Progressive beta cell dysfunction
Glycosuria
HNF4A-MODY
Progressive beta cell dysfunction
Fetal macrosomia
Neonatal hypoglycaemia
GCK-MODY
Stable beta cell function
Stable mildly raised glucose
HNF1B-MODY
Beta cell developmental defect
Exocrine pancreas deficiency
Other organ developmental defects
e.g kidney, uterus
Low-dose sulfonylureas
No treatment required
Insulin

MODY Probability Calculator

Please note work on this model is still in progress and further validation needs to be undertaken. **If viewing on a phone, you may need to rotate your phone horizontally to read all the outputs. Or you can download our app here.**

This is for use in patients diagnosed with diabetes under the age of 35 and was developed on a European Caucasian cohort. (Shields et al. 2012, Diabetologia)

Enter the clinical features of the patient in the form below and press the "Calculate Probability" button.

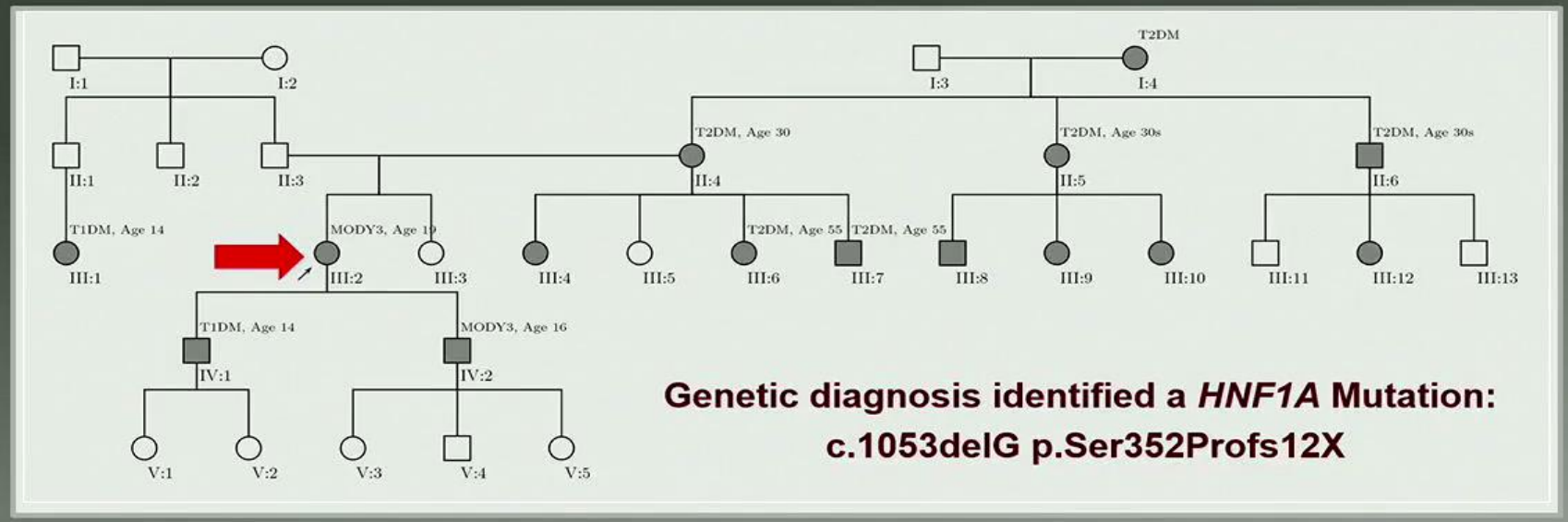
Enter Your Details

Age at diagnosis (years)	
Sex	○ Male ○ Female
Currently treated with insulin *or* OHA?	○ Yes ○ No
Time to Insulin Treatment (if currently treated with insulin)	○ Not currently treated with insulin ○ Within 6 months of diagnosis ○ Over 6 months after diagnosis
BMI (kg/m^2)	
HbA1c (%)	or mmol/mol
Current Age (yrs)	
Parent affected with diabetes?	○ Yes ○ No

Calculate Probability | Reset

Case 1

- 58 year old female initially found to be hyperglycemic at age 19 with fasting blood glucose of 130 mg/dL.
- BMI was 19 kg/m^2.
- BG retested at age 23 during pregnancy, and was diagnosed as having gestational diabetes and then type 2 diabetes mellitus.
- Initially diet-controlled, but transitioned between oral agents (including metformin and troglitazone) and insulin due to fluctuating diagnoses of gestational, type 1 and T2DM.
- Presented to a new endocrinologist's office at age 58. Mild-moderate insulin resistance: 0.87 units insulin/kg; using 90 units/day via insulin pump.
- Current weight 230 pounds and BMI 40.7kg/m^2.

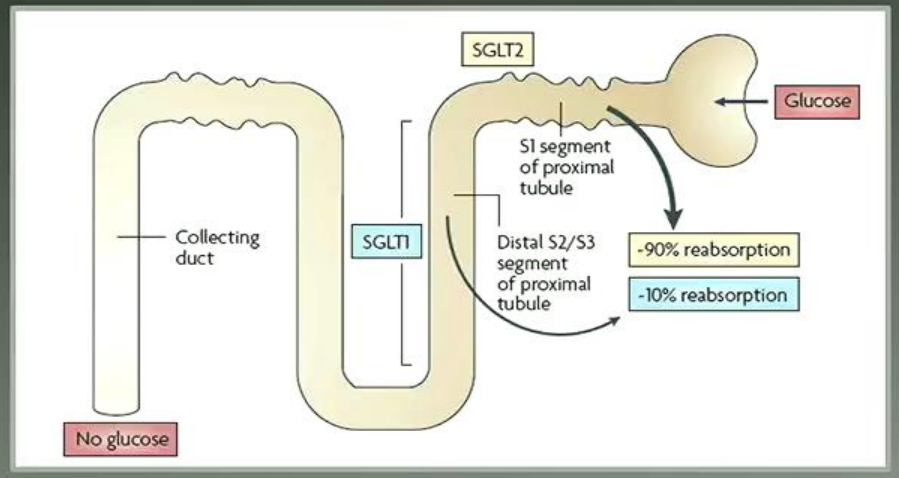


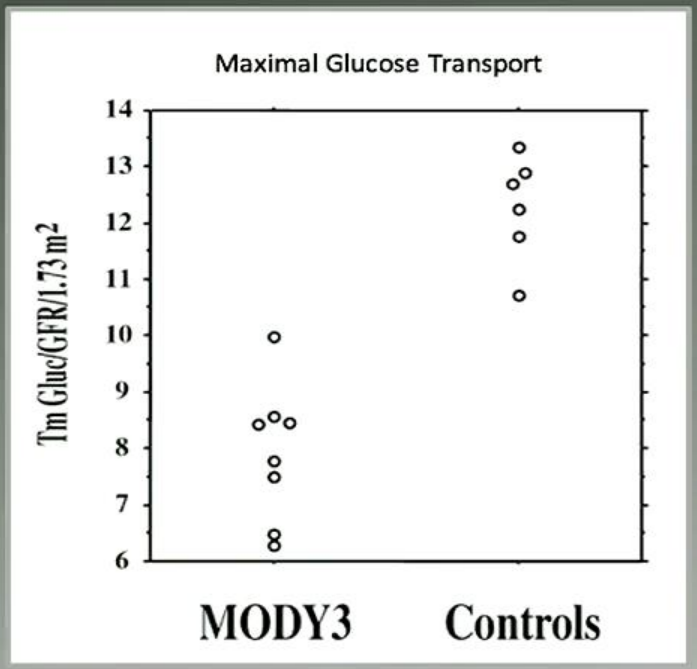
Genetic diagnosis identified a *HNF1A* Mutation:
c.1053delG p.Ser352Profs12X

1. Obesity doesn't always mean T2D
2. Inquire about your patient's **family history**
3. Genetic testing to confirm

THE UNIVERSITY OF CHICAGO MEDICINE
Kovler Diabetes Center

HNF1A and Renal Glucosuria



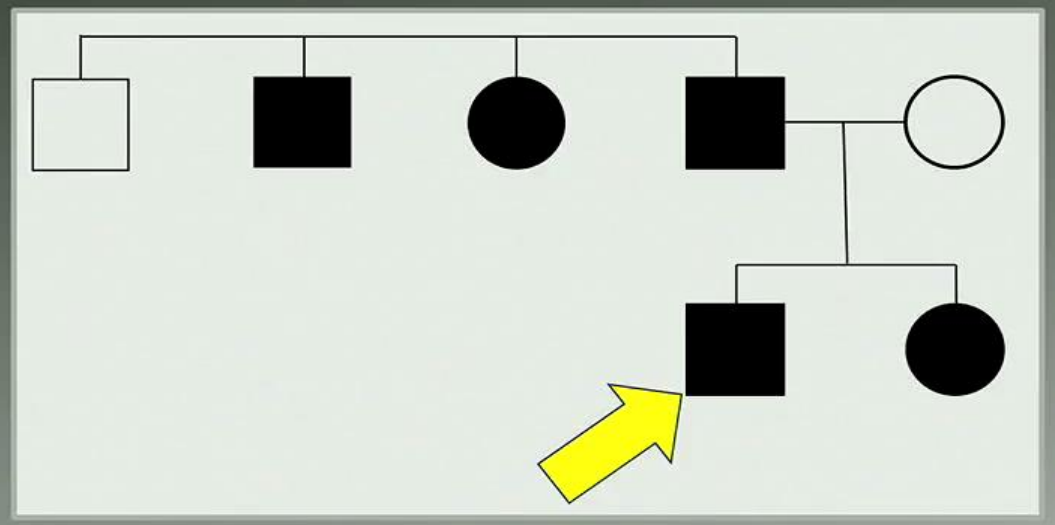


- MODY3 patients are characterized by reduced tubular reabsorption of glucose.
- The renal defect is due to reduced expression of the SGLT2 (2000).
- HNF1A directly controls SGLT2 gene expression.

Pontoglio M, et al. 2000

Case 2: Diabetes or hyperglycemia?

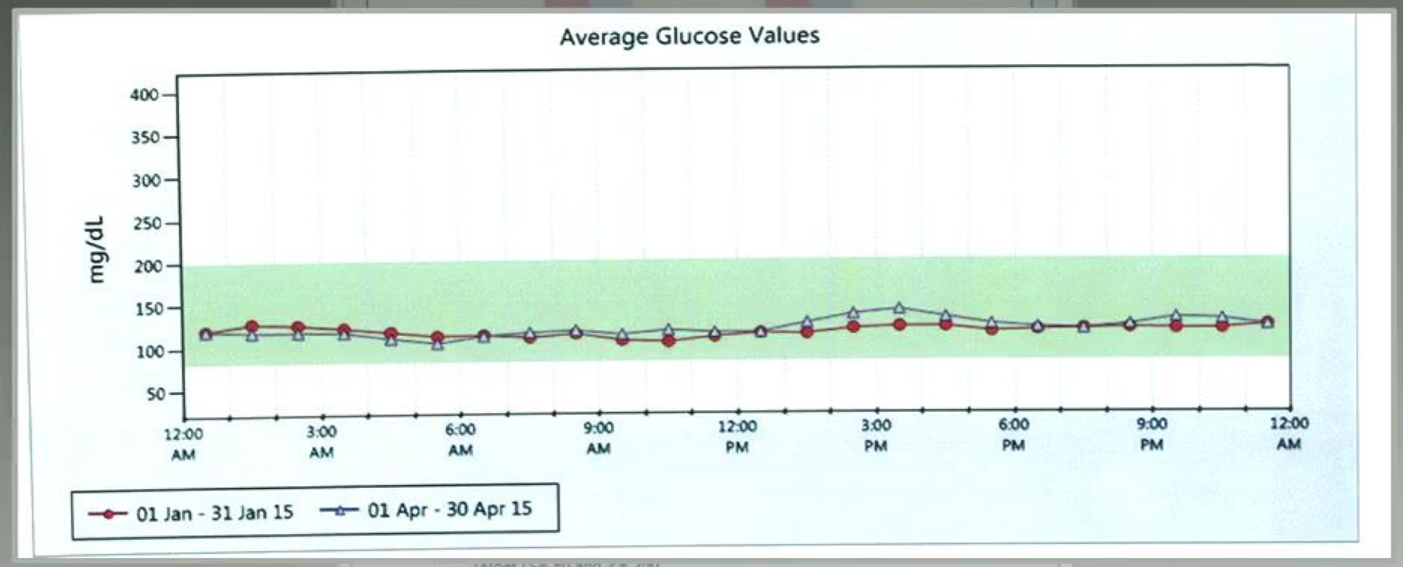
- Dx age 26
- FBG elevated: 124 mg/dL
- HbA1c ranges between **5.6% and 6.2%**
- BMI: 23.0 kg/m^2
- Diabetes autoantibody negative
- On insulin for 13 years, ~20 units per day (0.26 u/kg/day)



Genetic testing revealed GCK-MODY2: Thr168Asn

GCK: no treatment in required*

After 13 years, patient unplugged his insulin pump



THE UNIVERSITY OF CHICAGO MEDICINE
Kovler Diabetes Center

*Usually

GCK-MODY2: What you need to know

- GCK-MODY2 continues to be misdiagnosed and improperly treated, unnecessarily driving up the costs and complications.
- GCK-MODY2 can be accurately identified based on simple clinical criteria:
  - Stable elevated fasting glucose and A1c
  - Usually a family history that could include either type 1 or type 2 diagnoses
  - Autoantibody negative, usually non-obese
- Clinical genetic testing should be more readily available for the 1 in 1,000 individuals affected by GCK-MODY2.

THE UNIVERSITY OF CHICAGO MEDICINE
Kovler Diabetes Center

PRECISION MEDICINE

APPROCHE DU TYPAGE DU DIABETE EN CLUSTERS AU DIAGNOSTIC

NOUVELLE CLASSIFICATION SCANDINAVE

Lancet Diabetes Endocrinol 2018

Published Online
March 1, 2018
http://dx.doi.org/10.1016/
S2213-8587(18)30051-2

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*

- Nouvelle classification pourrait fournir un outil performant pour identifier au diagnostic les patients à haut risque de complications et proposer un traitement individualisé. (inspirer formes mono géniques du diabète qui guident les cliniciens pour un traitement optimal).
- Proposent 5 types, basée sur 6 paramètres : Age au diagnostic, BMI, A1c, GAD, dosage du peptide C → fonction cellules beta (HOMA2-B) et insulinoresistance (HOMA2-IR)
- Analyse comparative des 5 groupes : métabolique, génétique, clinique
- 4 populations originaires (Suède et Finlande)

CINQ CLUSTERS

	SAID = 6 % Severe AutoImmune Diabetes	SIDD = 17% Severe Insulin-Deficient Diabetes	SIRD = 15 % Severe Insulin-Resistance Diabetes	MOD = 21 % Mild Obesity-related Diabetes	MARD = 39 % Mild Age-Related Diabetes
Age de début	Jeune	Jeune			Plus avancé
BMI	Relativement bas	Relativement bas	Elevé	Elevé	Elevé
Contrôle métabolique	Mauvais	Mauvais		Mineur	Mineur
Déficit en insuline	+++	+++			
GAD	Positif	Négatif			
I-R (Index HOMA2-IR)			Elevée ↑↑	Bas ↓↓	Bas ↓↓

COMPARISON DES COMPLICATIONS

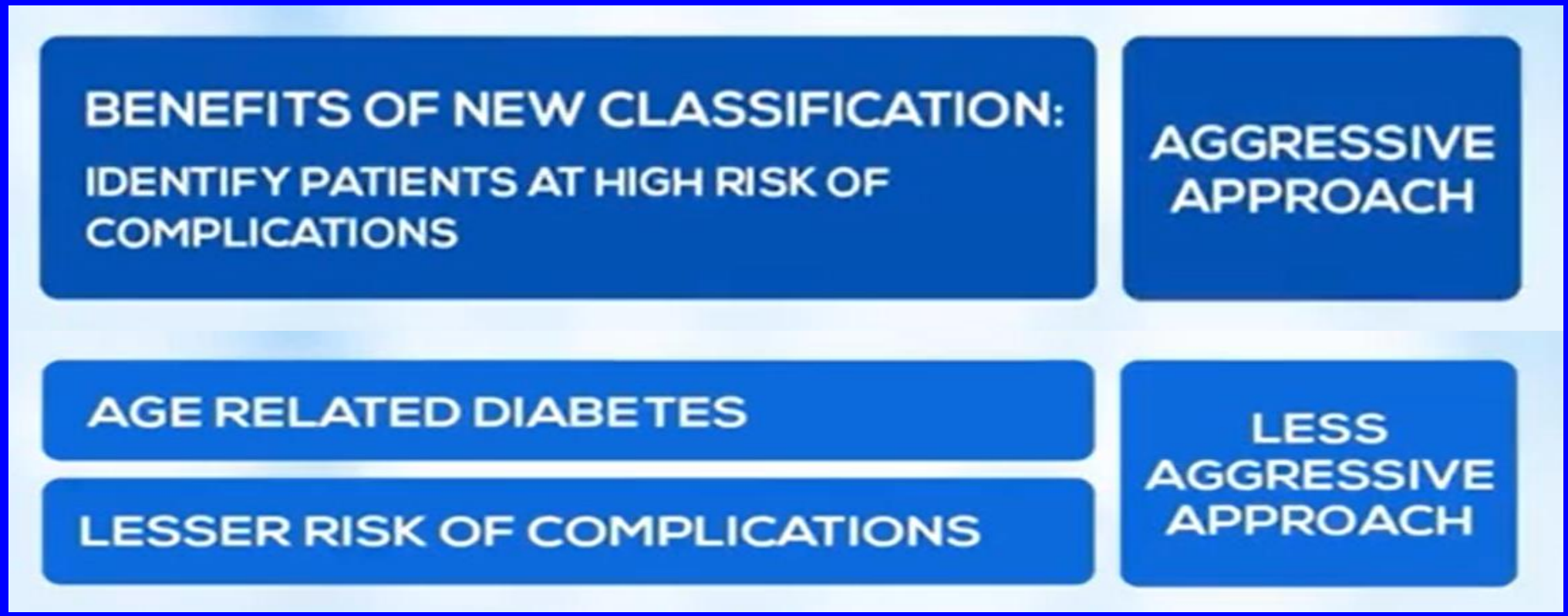
- **Risque IRC plus élevé cluster 3 «SIRD» = Insulino Resistant** (follow-up de 4 ans)
  - Stade 3 A (45- 59 ml/mn): **Risque > 2 fois** que le cluster 5
  - Stade 3 B (30-44 ml/mn):) : **Risque > 3 fo**is que le cluster 5
- Cluster 3 (IR) ont un risque plus élevé de développer une macroalubuminurie persistante (maladie rénale diabétique)

- Rétinopathie diabétique plus fréquente dans le cluster 2 par rapport aux autres clusters, confirmés dans 3 cohortes (ANDIS, ANDIU et SDR)

- Coronaropathie et AVC : pas de différence significative entre les clusters après ajustement sur âge et sexe

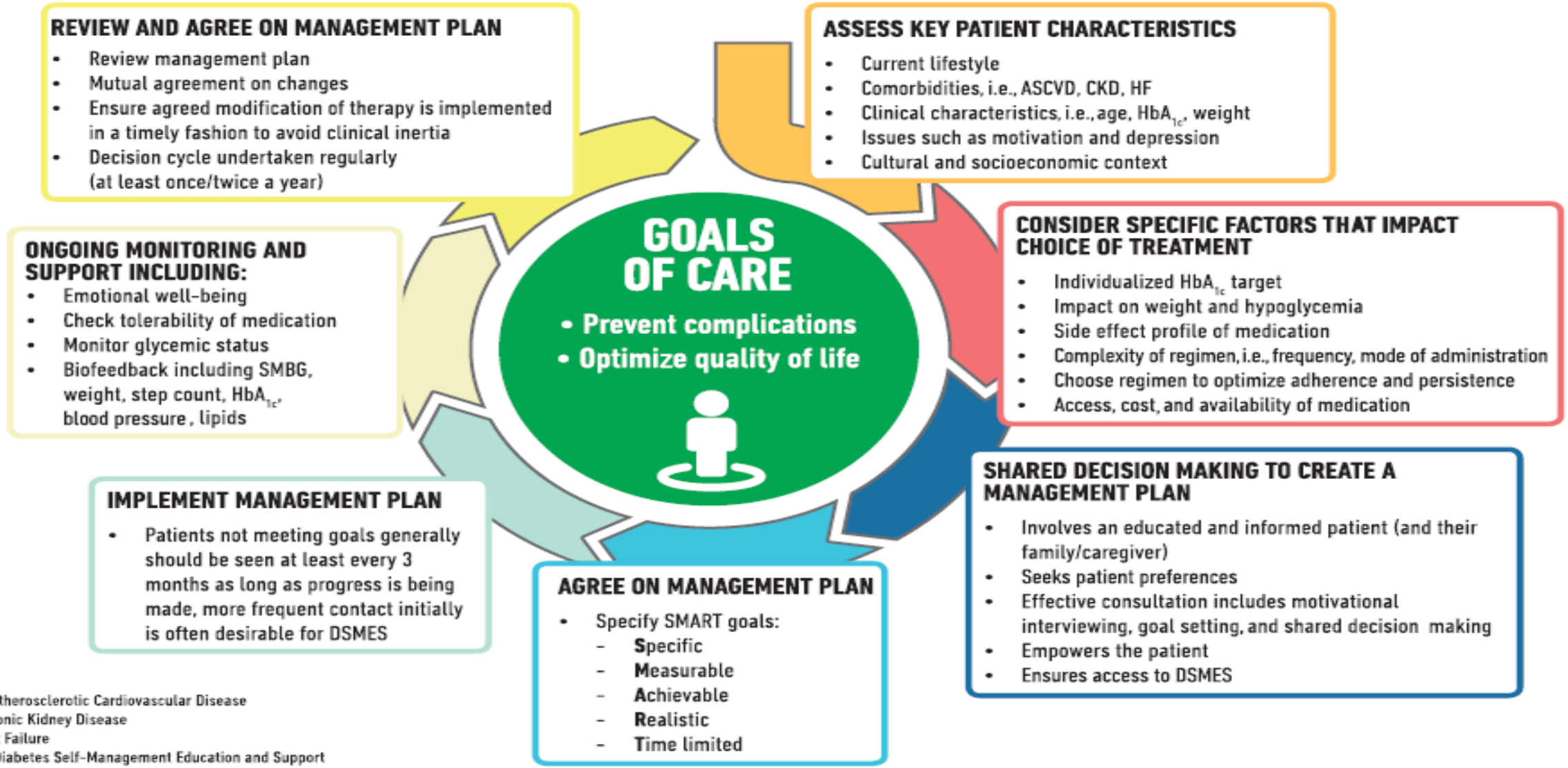
IMPLICATIONS

- This new substratification could change the way we think about type 2 diabetes and help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.



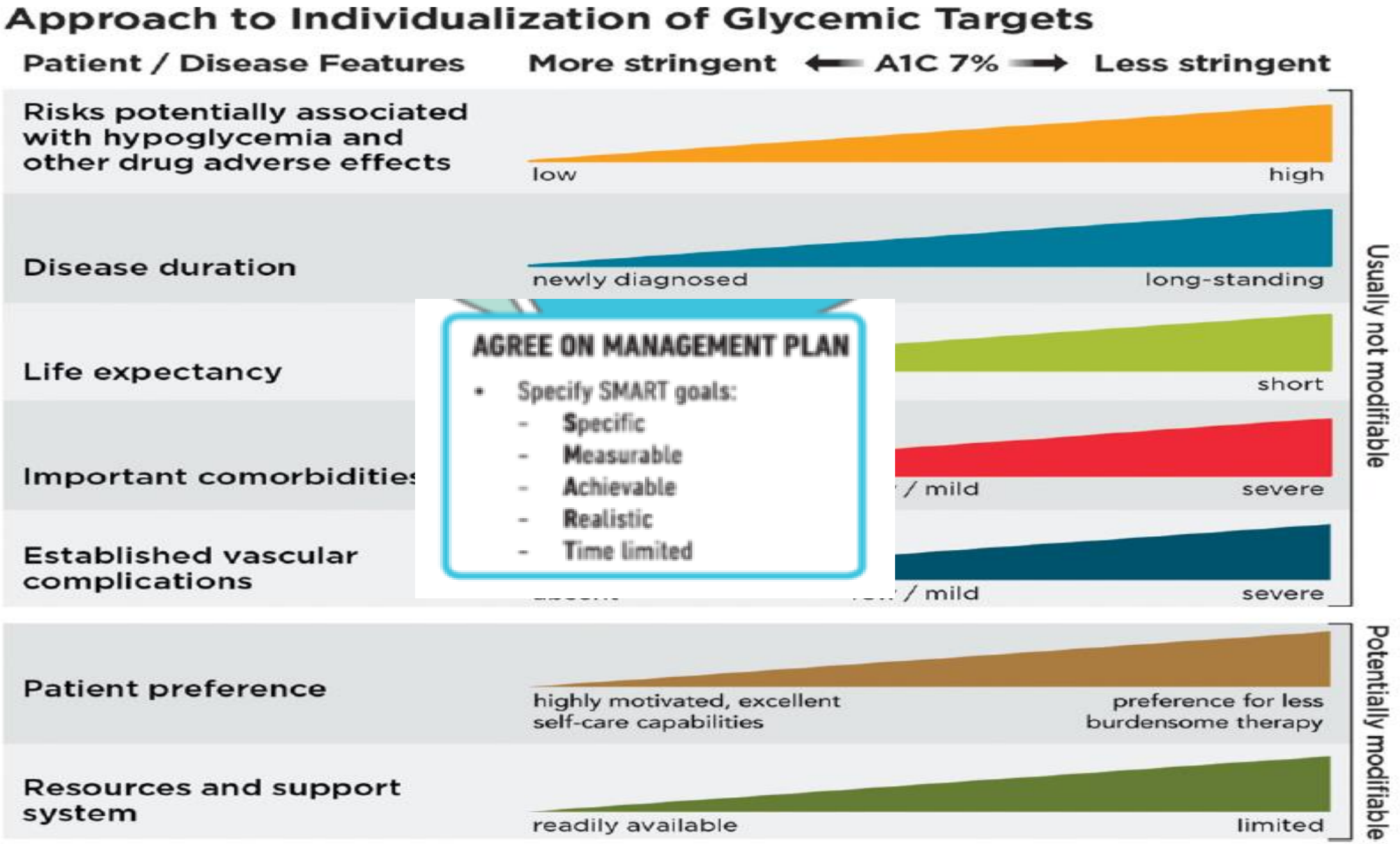
APPROCHE INDIVIDUATION DE L'OBJECTIF GLYCÉMIQUE

Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019;42(Suppl. 1):S61-S70



Diabetes Care 2019;42(Suppl. 1):S61–S70 | https://doi.org/10.2337/dc19-S006

A1C Goals

6.6 Less stringent A1C goals (**such as <8%)** may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B

6.7 Reassess glycemic targets over time based on the criteria in **Fig. 6.1** or, in older adults, **Table 12.1**. E

Glycemic Targets: *Standards of Medical Care in Diabetes - 2019*. *Diabetes Care* 2019;42(Suppl. 1):S61-S70

Table 12.2—Considerations for treatment regimen simplification and deintensification/deprescribing in older adults with diabetes (39,55)

Patient characteristics/ health status	Reasonable A1C/ treatment goal	Rationale/considerations	When may regimen simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	A1C <7.5% (58 mmol/mol)	• Patients can generally perform complex tasks to maintain good glycemic control when health is stable • During acute illness, patients may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc.	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	A1C <8.0% (64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication regimen	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If unable to manage complexity of an insulin regimen • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling patients receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C Glucose target: 100–200 mg/dL (5.55–11.1 mmol/L)	• Glycemic control is important for recovery, wound healing, hydration, and avoidance of infections • Patients recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the patient will receive at home	• If treatment regimen increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication regimen during the rehabilitation	• If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (long-term care or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	A1C <8.5% (69 mmol/)†	• No benefits of tight glycemic control in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• If on an insulin regimen and the patient would like to decrease the number of injections and fingerstick blood glucose monitoring events each day • If the patient has an inconsistent eating pattern	• If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern • If taking any medications without clear benefits
Patients at end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life	• If there is pain or discomfort caused by treatment (e.g., injections or fingersticks) • If there is excessive caregiver stress due to treatment complexity	• If taking any medications without clear benefits in improving symptoms and/or comfort

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia

- Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
- Impaired kidney or hepatic function
- Longer duration of diabetes
- Frailty and older age
- Cognitive impairment
- Impaired counterregulatory response, hypoglycemia unawareness
- Physical or intellectual disability that may impair behavioral response to hypoglycemia
- Alcohol use
- Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)

See references 114–118.

Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019;42(Suppl. 1):S61-S70

DEFINE TYPE 2 DIABETES SUBGROUPS BASED ON DIFFERENTIAL TREATMENT RESPONSE TO DRUGS

VARIATION DE LA RÉPONSE INDIVIDUELLE AUX DIFFÉRENTS TRAITEMENTS DANS LE DIABÈTE

Studies to define subgroups based on differential treatment response to drugs

- ✓ Insulin-treated type 2 patients with islet autoantibodies or low C-peptide who do not respond to GLP-1 receptor agonists. **[Diabetes Care 2016;39:250–257]**

- ✓ A recent example of the successful implementation of this approach is the use of sex and BMI data for identification of patients with a preferential response to thiazolidinediones (obese female) or sulfonylureas (slim male). **[Diabetes Care 2018;41:1844–1853]**

- ✓ Clinical markers of IR are associated with altered short and long-term glycemic response to DPP-4 inhibitors therapy.

[Diabetes Care 2018;41:705–712]

Markers of β-Cell Failure Predict Poor Glycemic Response to GLP-1 Receptor Agonist Therapy in Type 2 Diabetes

Angus G. Jones,[1] Timothy J. McDonald,[1] Beverley M. Shields,[1] Anita V. Hill,[1] Christopher J. Hyde,[2] Bridget A. Knight,[1] and Andrew T. Hattersley,[1] for the PRIBA Study Group*

Diabetes Care 2016;39:250–257 | DOI: 10.2337/dc15-0258

RESEARCH DESIGN AND METHODS

620 participants with T2D and HbA1c > 7.5%, commencing GLP-1RA therapy were assessed response to therapy over 6 months. We assessed the association between baseline clinical measurements associated with b-cell failure and glycemic response (primary outcome HbA1c change 0–6 months).

Table 2—The relationship between baseline markers of β-cell function and HbA_{1c} changes after GLP-1RA therapy

	Association with HbA_{1c} change (mmol/mol)			
Baseline characteristic	Regression coefficient (95% CI)*	Standardized regression coefficient (95% CI)**	*T* statistic***	Significance (*P*)
Diabetes duration (years)	0.27 (0.08, 0.46)	0.10 (0.03, 0.18)	2.7	0.006
Insulin cotreatment	8.5 (5.3, 11.7)	—	5.2	<0.001
Fasting C-peptide (nmol/L)	−3.2 (−5.2, −1.2)	−0.12 (−0.19, −0.04)	−3.1	0.002
UCPCR (nmol/mmol)	−0.56 (−1.0, −0.12)	−0.10 (−0.18, −0.02)	−2.5	0.01
Autoantibody (GAD/IA2) positive	10.0 (3.1, 16.8)	—	2.8	0.005

RESULTS

Reduced glycemic response to GLP-1RAs was associated with longer duration of diabetes, insulin cotreatment, lower fasting C-peptide, lower postmeal urine C peptide–to–creatinine ratio, and positive GAD or IA2 islet autoantibodies .

CONCLUSIONS

Clinical markers of low b-cell function are associated with reduced glycemic response to GLP-1RA therapy. C-peptide and islet autoantibodies represent potential biomarkers for the stratification of GLP-1RA therapy in insulin-treated diabetes.

Diabetes Care 2016;39:250–257

Sex and BMI Alter the Benefits and Risks of Sulfonylureas and Thiazolidinediones in Type 2 Diabetes: A Framework for Evaluating Stratification Using Routine Clinical and Individual Trial Data

John M. Dennis,[1] William E. Henley,[1] Michael N. Weedon,[2] Mike Lonergan,[3] Lauren R. Rodgers,[1] Angus G. Jones,[4,5] William T. Hamilton,[2] Naveed Sattar,[6] Salim Janmohamed,[7] Rury R. Holman,[8,9] Ewan R. Pearson,[3] Beverley M. Shields,[4] and Andrew T. Hattersley,[4,5] on behalf of the MASTERMIND Consortium*

Diabetes Care 2018;41:1844–1853 | https://doi.org/10.2337/dc18-0344

RESEARCH DESIGN AND METHODS

We studied 22,379 patients starting sulfonylurea or thiazolidinedione therapy in the U.K. CPRD to identify features associated with increased 1-year HbA1c fall with one therapy class and reduced fall with the second. We then assessed whether prespecified patient subgroups defined by the differential clinical factors showed differing 5-year glycemic response and side effects with sulfonylureas and thiazolidinediones using individual randomized trial data from ADOPT (first-line therapy, n = 2,725) and RECORD (second-line therapy, n = 2,222). Further replication was conducted using routine clinical data from GoDARTS (n = 1,977).

RESULTS

In CPRD, male sex and lower BMI were associated with greater glycemic response with sulfonylureas and a lesser response with thiazolidinediones (both $P < 0.001$). In ADOPT and RECORD, non obese males had a greater overall HbA1c reduction with sulfonylureas than with thiazolidinediones ($P < 0.001$); in contrast, obese females had a greater HbA1c reduction with thiazolidinediones than with sulfonylureas ($P < 0.001$). Weight gain and edema risk with thiazolidinediones were greatest in obese females.

CONCLUSIONS

Patient subgroups defined by sex and BMI have different patterns of benefits and risks on thiazolidinedione and sulfonylurea therapy. Subgroup-specific estimates can inform discussion about the choice of therapy after metformin for an individual patient. Our approach using routine and shared trial data provides a framework for future stratification research in type 2 diabetes.

Diabetes Care 2018;41:1844–1853

Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-term Glycemic Response to DPP-4 Inhibitor Therapy

John M. Dennis,[1] Beverley M. Shields,[2] Anita V. Hill,[2] Bridget A. Knight,[2] Timothy J. McDonald,[2,3] Lauren R. Rodgers,[1] Michael N. Weedon,[4] William E. Henley,[1] Naveed Sattar,[5] Rury R. Holman,[6] Ewan R. Pearson,[7] Andrew T. Hattersley,[2] and Angus G. Jones,[2] on behalf of the MASTERMIND Consortium

Diabetes Care 2018;41:705–712 | https://doi.org/10.2337/dc17-1827

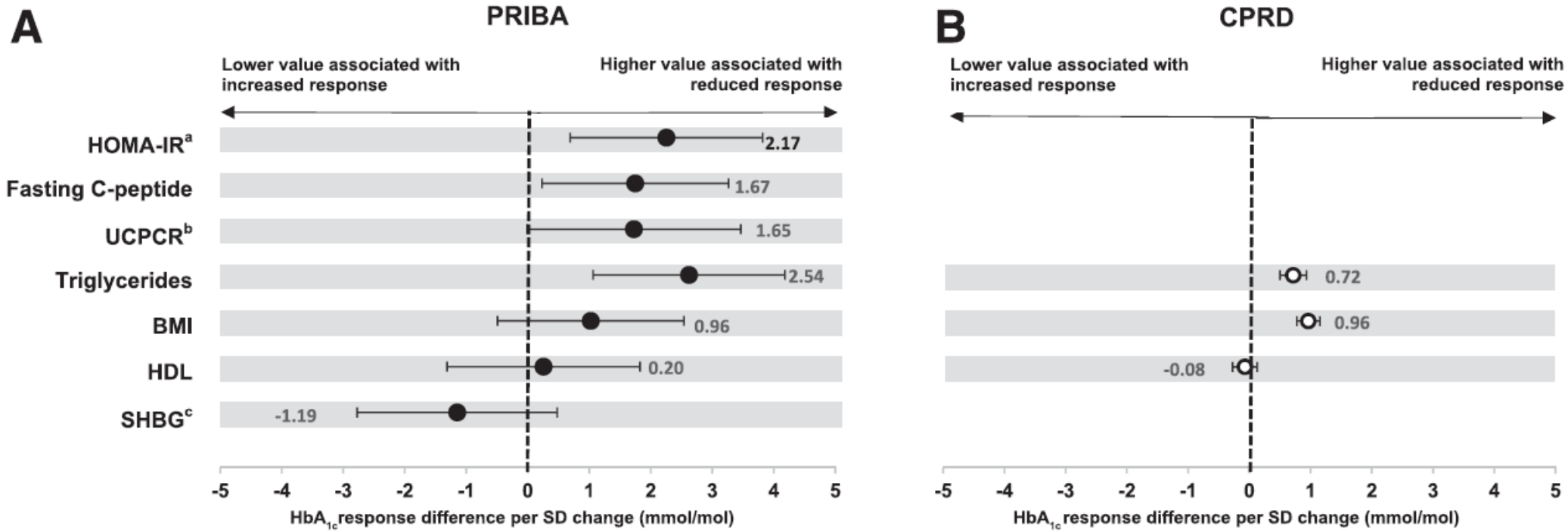
OBJECTIVE : We examined if measures of insulin resistance and secretion were associated with glycemic response to dipeptidyl peptidase 4 (DPP-4) inhibitor therapy.

RESEARCH DESIGN AND METHODS : We evaluated whether markers of insulin resistance and insulin secretion were associated with 6-month glycemic response in a prospective study of non insulin treated participants starting DPP-4 inhibitor therapy [PRIBA study; n = 254), with replication for routinely available markers in U.K. electronic health care records [CPRD; n = 23,001). In CPRD, we evaluated associations between baseline markers and 3-year durability of response. To test the specificity of findings, we repeated analyses for glucagon-like peptide 1 (GLP-1) receptor agonists (PRIBA, n = 339; CPRD, n = 4,464).

RESULTS

In PRIBA, markers of higher insulin resistance (higher fasting C-peptide [P = 0.03], HOMA2 insulin resistance [P = 0.01], and triglycerides [P < 0.01]) were associated with reduced 6-month HbA1c response to DPP-4 inhibitors. In CPRD, higher triglycerides and BMI were associated with reduced HbA1c response (both P < 0.01). A subgroup defined by obesity and high triglycerides (> 2g/L) had reduced 6-month response in both data sets (In CPRD, the obese, high triglycerides subgroup also had less durable response. There was no association between markers of IR and response to GLP-1.

Diabetes Care 2018;41:705–712

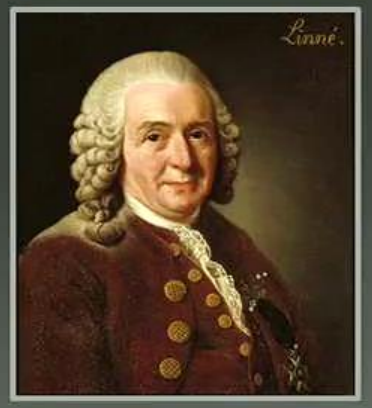


[a] HOMA2 measured insulin resistance [b] UCPCR = post meal urine C-peptide Creatinine ratio [c] SHBG = sex-hormone binding globulin

CONCLUSIONS

Markers of higher insulin resistance are consistently associated with reduced glycemic response to DPP-4 inhibitors. This finding provides a starting point for the application of a precision diabetes approach to DPP-4 inhibitor therapy.

Diabetes Care 2018;41:705–712



“The first step in wisdom is to know the things themselves; this notion consists in having a true idea of the objects; objects are distinguished and known by classifying them methodically and giving them appropriate names. Therefore, classification and name-giving will be the foundation of our science”

— Carolus Linnaeus
***Systema Naturae* (1735)**

MESSAGES REFLEXIONS ADA PRESIDENT

- I asked you to resolve to see every patient with diabetes in your practice with new eyes.
- Why does this person in front of me have diabetes ?
- What about the family ? Did you think about the family history ? Did you really take a minute to review the family history ?
- Can you incorporate such thinking right now ?
- Starting to incorporate the key elements of precision medicine could be a transformational event for both you and your patients persons with diabetes?
- Does your patient have beta cell failure, insulin resistance, liver disease or a monogenic cause ?
- Can that knowledge affect testing and therapy to improve outcomes in a cost effective way ? We must find out

[Louis H. Philipson, President Medicine and Science, ADA 2019]

MY MESSAGES TO TAKE HOME

- Typage précis du diabète au diagnostic.
- Hétérogénéité du diabète →Clusters→ Identifier les diabétiques à haut risque de complications.
- Utiliser des marqueurs bio-cliniques accessibles en pratique courante pour le typage du diabète au diagnostic (IR ++++) et immunologie (GAD)
- Diagnostiquer les diabètes mono géniques (MODY)= implications thérapeutiques
- Individualisation des objectifs glycémiques
- Adapter le choix des antidiabétiques en fonction des paramètres du patient qui prédisent le mieux la bonne réponse au traitements.
- SAFETY ++++


That's all Folks!
THANK YOU