Precision medicine in type 2 diabetes:

There is (much) more work to do

David M. Nathan, MD
MGH Diabetes Research Center, Harvard Medical School

Rachmiel Levine-Arthur Riggs Diabetes Research Symposium,
Pasadena, CA
September 21, 2024

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Debate: Precision Medicine in Type 2 Diabetes: There is More (Much More) Work to Do

David M. Nathan, MD

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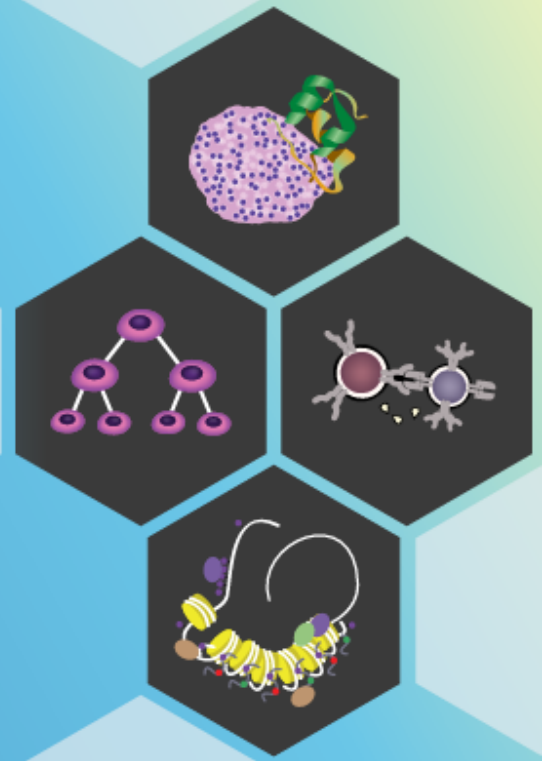
Massachusetts General Hospital

Professor of Medicine, Harvard Medical School



Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

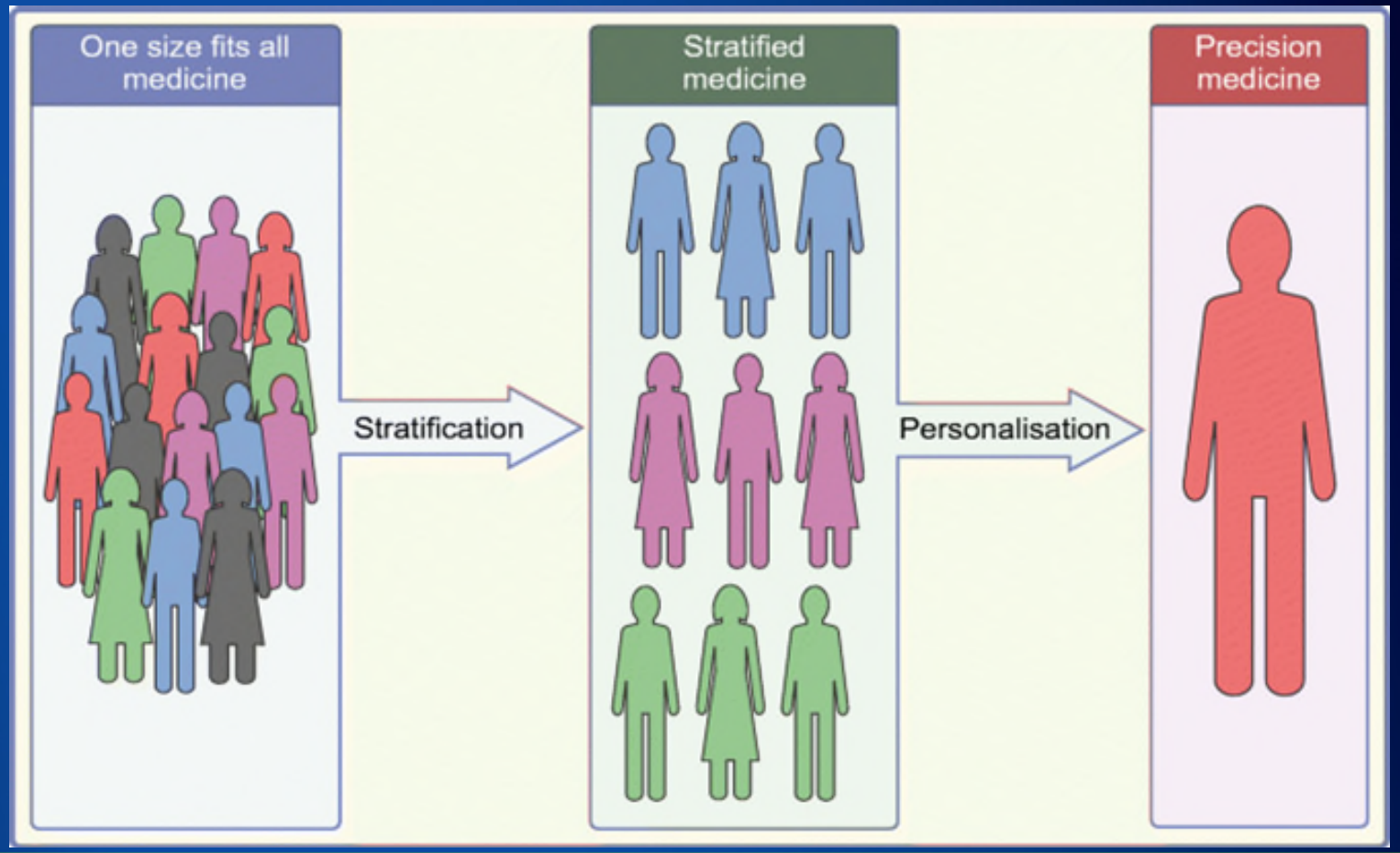
The following CLC & IB components will be addressed in this presentation:

- *Address precision medicine or the individualization of therapy of type 2 diabetes, focusing on the heterogeneity of type 2 diabetes and so will include discussion of genetic and social and other determinants associated with diabetes and its treatment.*
- *Discuss differences in treatment of diabetes associated with implicit bias based on race.*

Precision (or Personalized) Medicine

"…a medical model that separates people into different groups- with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease."

"Providing the right therapy for the right patient at the right time"



Precision (or Personalized) Medicine

CONSENSUS REPORT

Precision medicine in diabetes: a Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Wendy K. Chung[1,2] · Karel Erion[3] · Jose C. Florez[4,5,6,7,8] · Andrew T. Hattersley[9] · Marie-France Hivert[5,10] · Christine G. Lee[11] · Mark I. McCarthy[12,13,14] · John J. Nolan[15] · Jill M. Norris[16] · Ewan R. Pearson[17] · Louis Philipson[18,19] · Allison T. McElvaine[20] · William T. Cefalu[11] · Stephen S. Rich[21,22] · Paul W. Franks[23,24]

Diabetologia 2020; 63:1671

Defines and discusses precision diagnostics and precision therapeutics

History of Diabetes Nosology

How Have We Classified Diabetes

Antiquity

1500 BC 600 BC 100AD

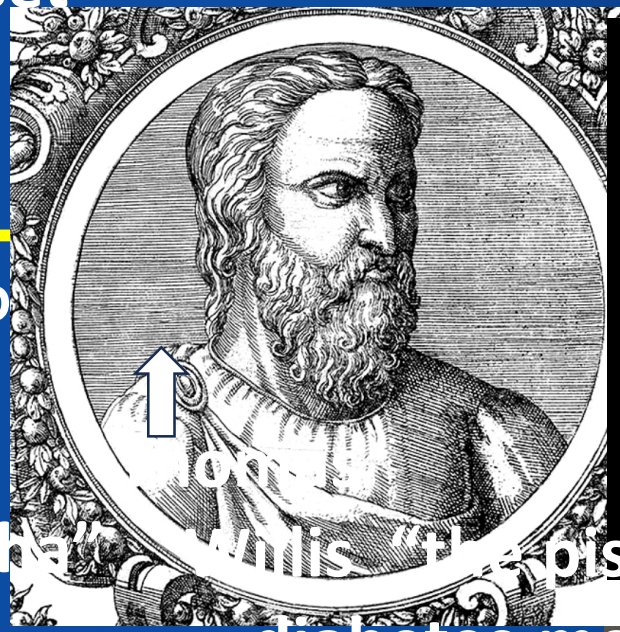
Ebers Papyrus

Sashruta

"madhumeha"

Juvenile vs

Adult-onset



Arateus- διαβαίνω

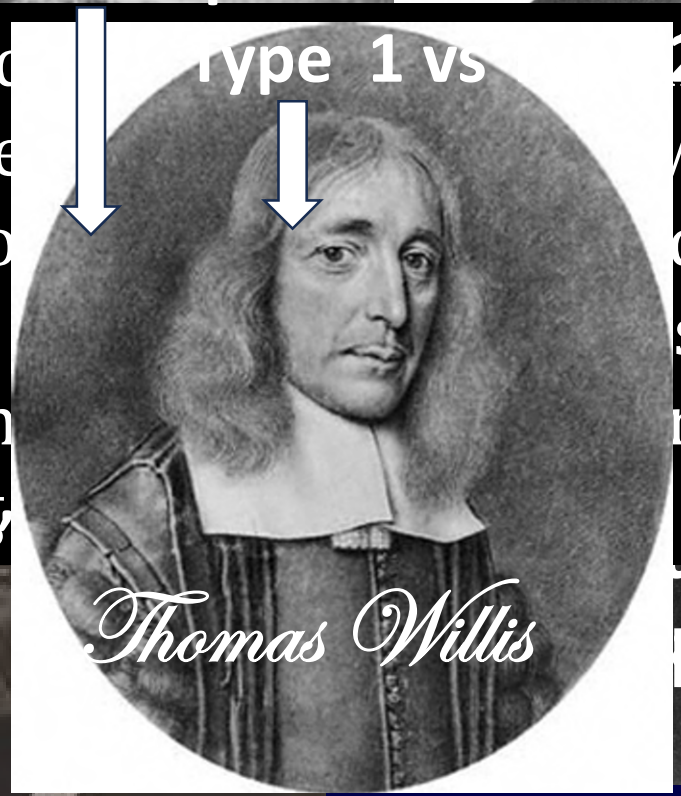
Insulin dependent vs

Non-insulin dependent

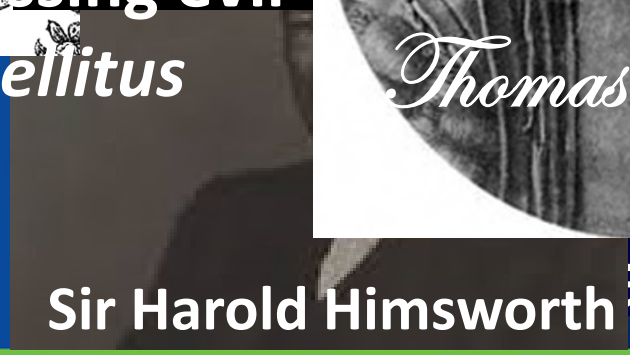
"...life is c... Type 1 vs ...2; thirst;
excessive ...wever, is
dispropo... ...quantity
of urine, ...sed; and
one cann... ...rom
drinking...

...pissing evil

diabetes mellitus



...tic diabetes"



Sir Harold Himsworth

History of Diabetes Nosology

Where are we now?

ADA 2024

NDDG/WHO
Type 1 vs Type 2

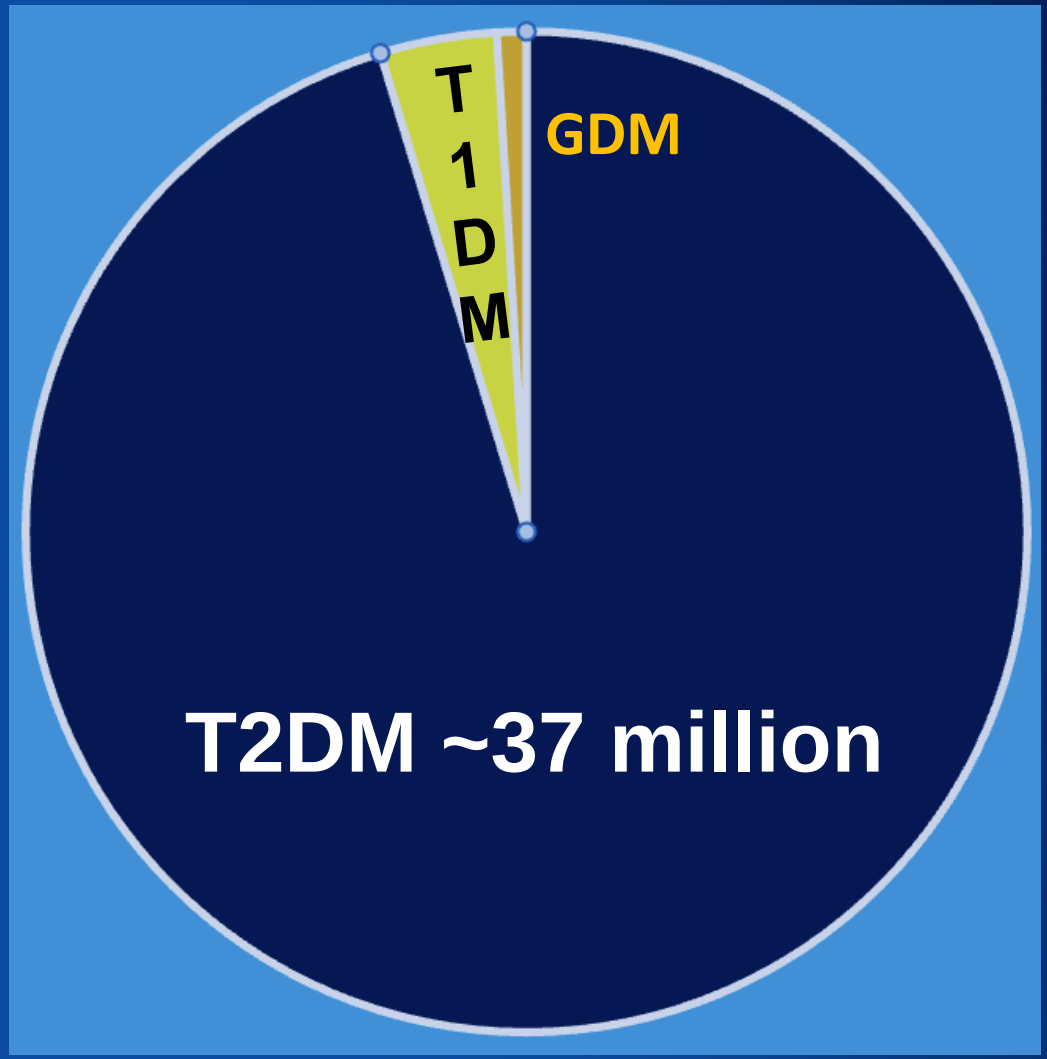
1500 BC | 600 BC | 100AD | 1650 | 1889 | 1936 | 1979/1980 | 2024

2. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Precision Medicine???

After >3000 years of combined Eastern and Western medical care, the major advance in precision medicine has been the separation of Type 1 and Type 2 diabetes, recognizing their different etiologies, pathophysiology and treatments.

Current Diabetes Epidemiology-US



T1D ~1.5 million
GDM- ~10% of pregnancies (~350,000)
T2D ~37 million

Precision Medicine???

Currently, >99% patients with “Type 2 diabetes” are treated as if they have the same disease despite aspirational intentions.

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

ADA Standards of Care in Diabetes-2024

9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences

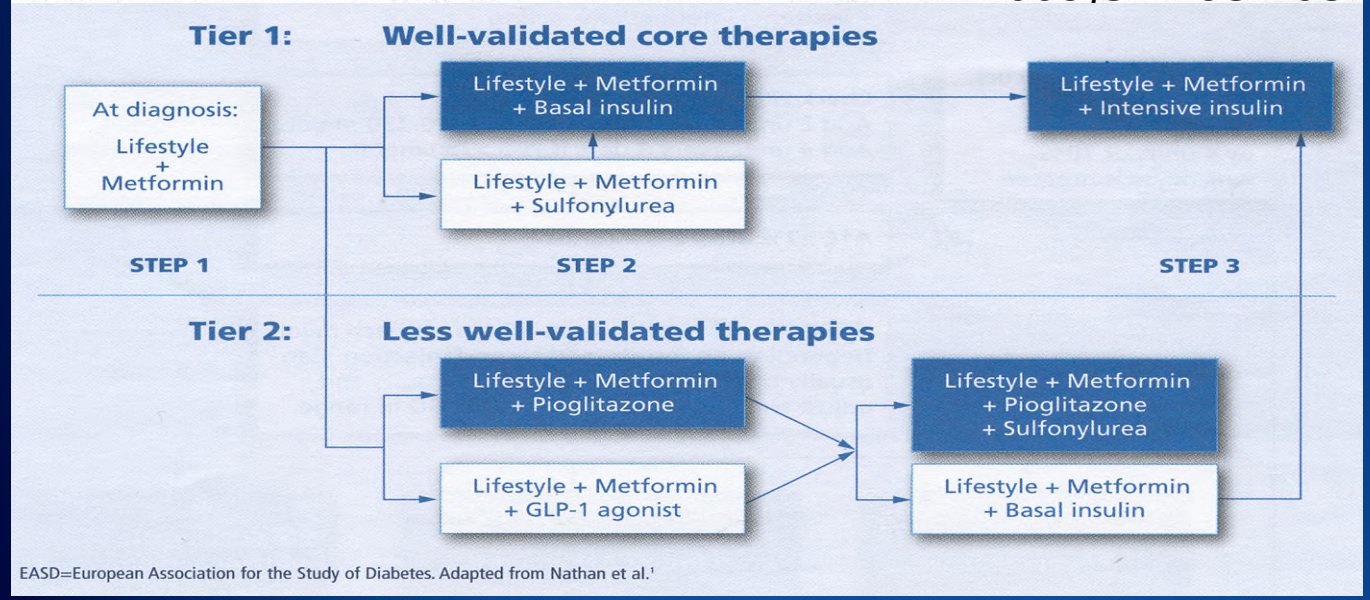
First Consensus Algorithm

Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

D. M. Nathan · J. B. Buse · M. B. Davidson · E. Ferrannini · R. R. Holman · R. Sherwin · B. Zinman

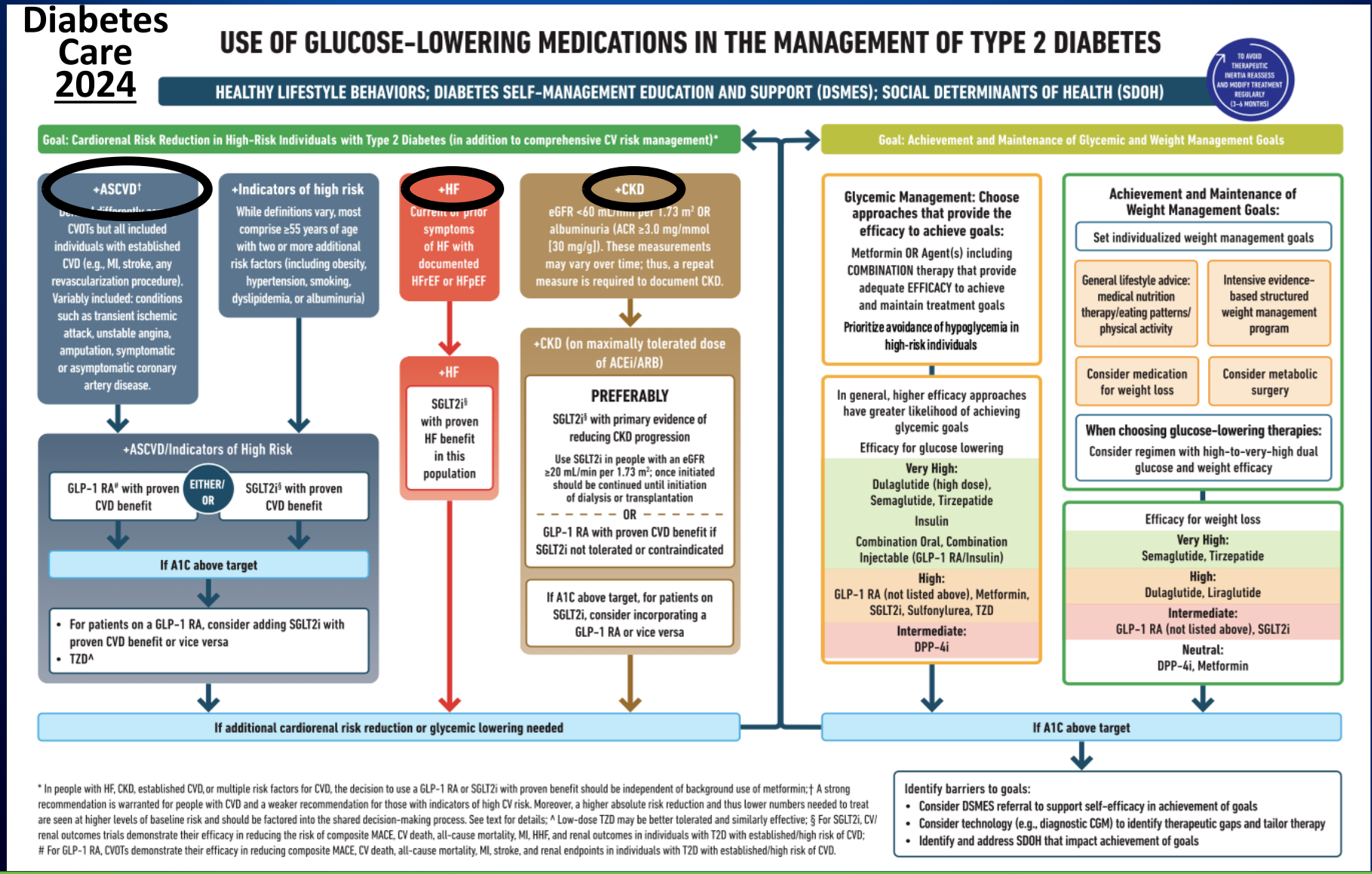
First published 2006, revised
Diabetologia 2009; 52:17-30
Diabetes Care 2009;32:193-203



EASD=European Association for the Study of Diabetes. Adapted from Nathan et al.[1]

Almost no mention of individualization of treatment of type 2 diabetes.

ADA Algorithm-2024



The current attempts to target therapy are <u>based on co-morbidities</u> and newly identified attributes of diabetes medications (discovered accidentally and not by design).

Current Approaches to Precision Medicine

Best examples to date:
Treatment of MODY1 and MODY3 (HNF4α and HNF1α) with sulfonylureas and no need to treat MODY2 (GCK) outside of pregnancy. MODY1-3 represent >90% of monogenic DM, but <1% T2.

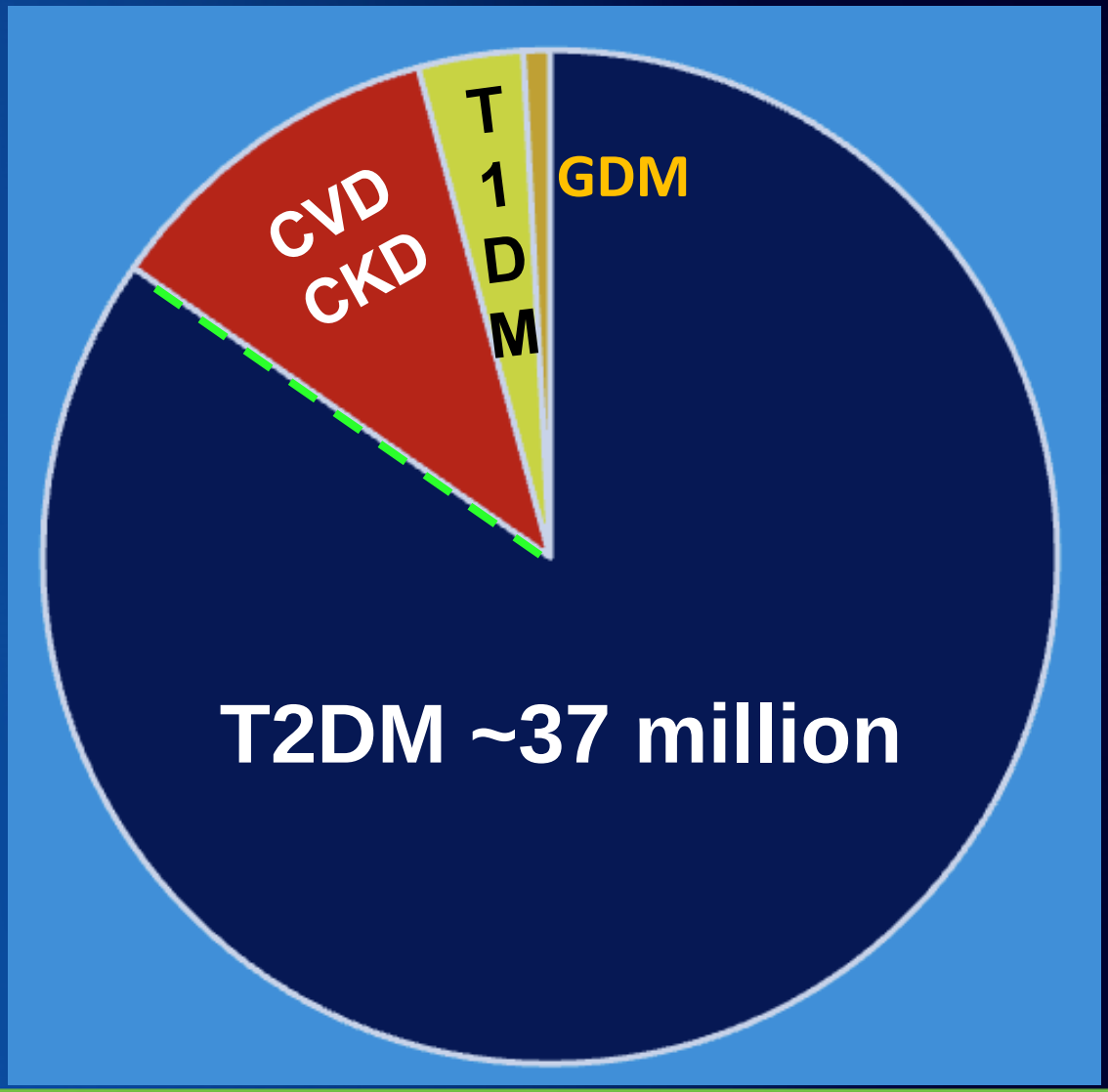
Current Diabetes Epidemiology-US

Best Case Scenario
for individualized therapy in 2024

- **~15% with CVD/CKD**
- **<1% with MODY 1-3**

Currently, most phenotyping that directs precision medicine in T2DM occurs after morbidity has occurred.

Majority of T2DM not helped by precision medicine.



More Sensible Approaches to Precision Medicine

Step 1: Recognize and identify heterogeneity of "Type 2 diabetes"

Subtypes by:

- **a) Genetics**
- **b) Demographics**
- **c) Phenotyping**
  - **i. Pathophysiology**
  - **ii. Outcomes**
- **d) AI approaches**

Step 2: Apply interventions across different subtypes to determine whether different therapies have differential effects across sub-types.

Current Approaches to Precision Medicine

Best genetic examples to date:
Treatment of MODY1 and MODY3 (HNF4α and HNF1α) with sulfonylureas and no need to treat MODY2 (GCK) outside of pregnancy.
MODY1-3 represent >90% of monogenic DM, but <1% T2.

However, the vast majority of T2 is polygenic.

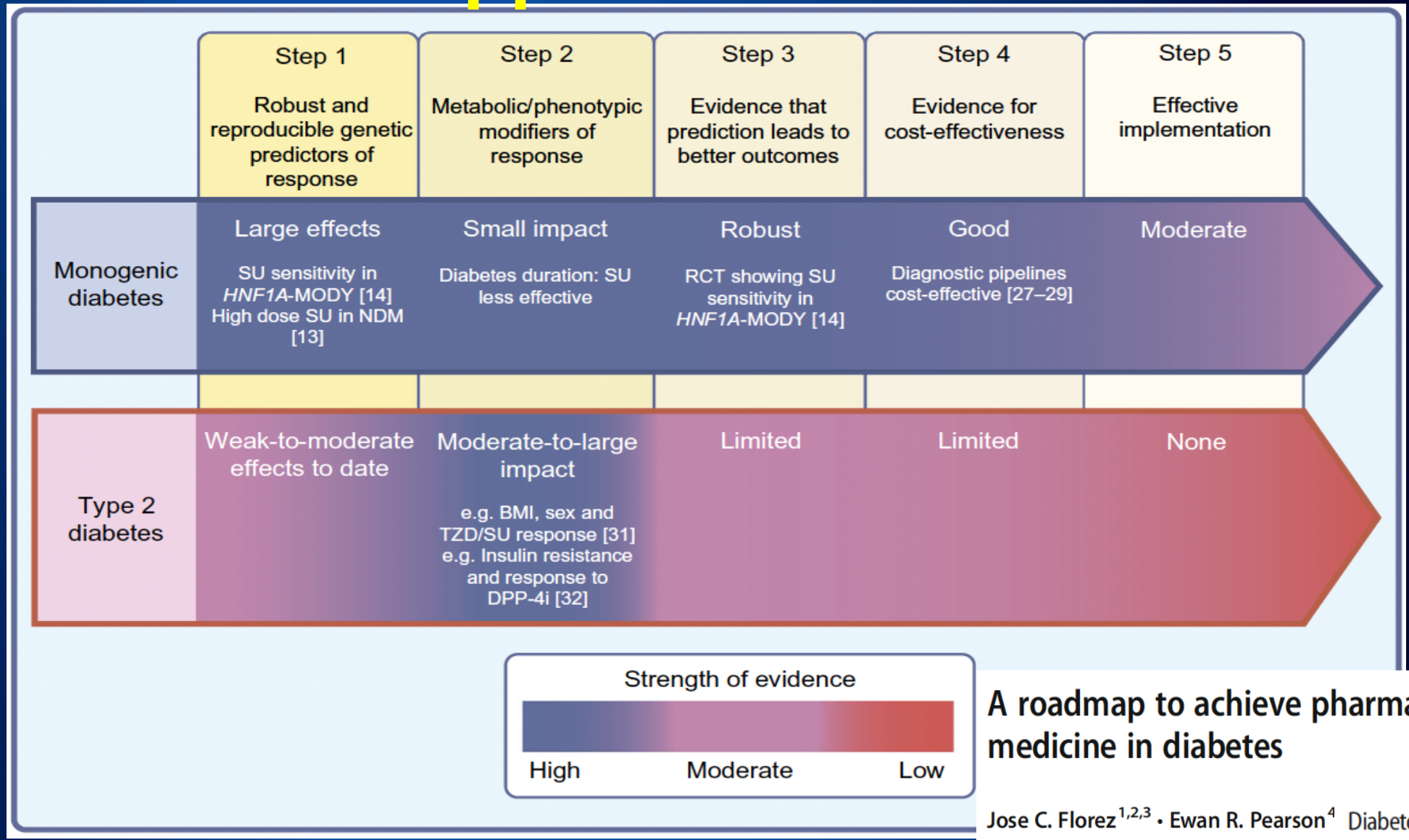
RADIANT - NIDDK sponsored study to examine "atypical" forms of T2.

Heterogeneity of T2DM- RFA DK-23-019 "*Integration of Novel Measures for Improved Classification of Type 2 Diabetes*".

More Sensible Approaches to Precision Medicine

1. Recognize and identify heterogeneity of “Type 2 diabetes” Subtypes by:
   a) Genetics- pathogenesis and response to therapy
   b) Demographics
   c) Phenotyping
      i. Pathophysiology
      ii. Outcomes
   d) AI approaches
2. Apply interventions across different subtypes to determine whether different therapies have differential effects across sub-types.

More Sensible Approaches to Precision Medicine



A roadmap to achieve pharmacological precision medicine in diabetes

Jose C. Florez[1,2,3] · Ewan R. Pearson[4] Diabetologia (2022) 65:1830–1838

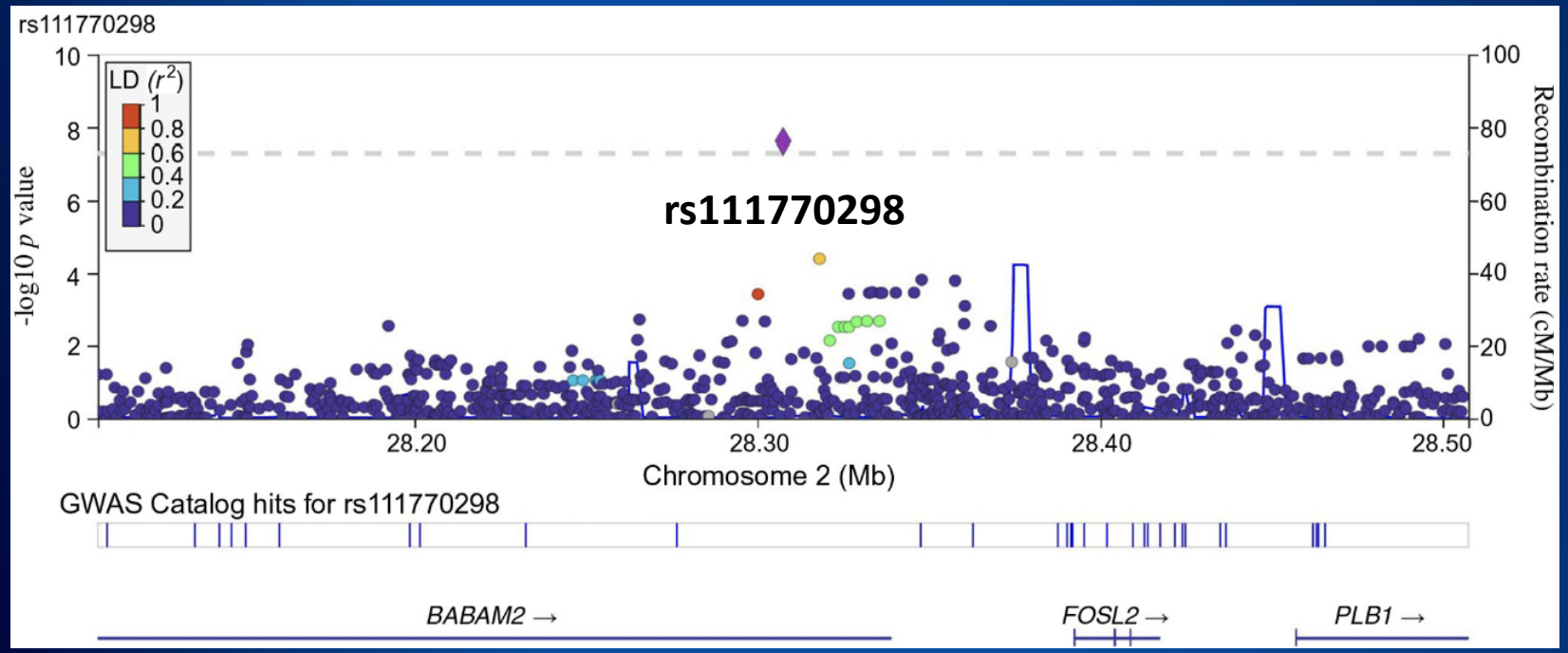
Genome-wide association analysis identifies ancestry-specific genetic variation associated with acute response to metformin and glipizide in SUGAR-MGH

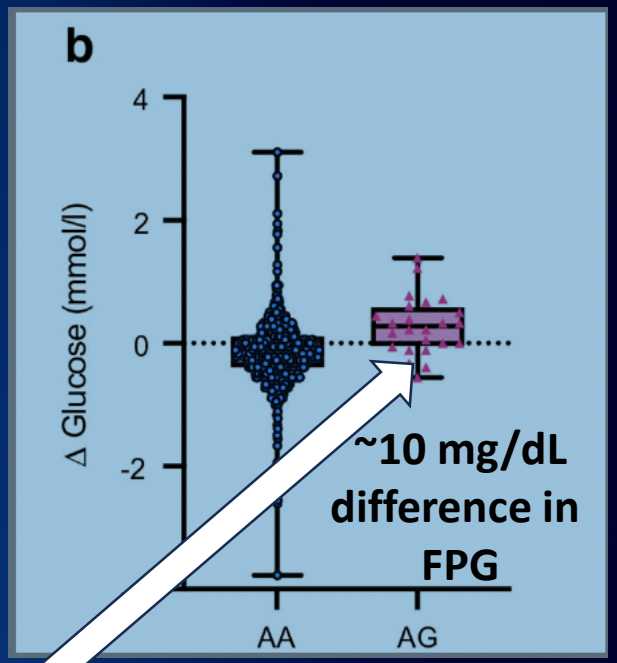
Josephine H. Li[1,2,3,4], Laura N. Brenner[1,3,4,5], Varinderpal Kaur[1,2,3], Katherine Figueroa[1,3], Philip Schroeder[1,2,3], Alicia Huerta-Chagoya[1,2,3],
MAGIC Investigators,
Diabetes Prevention Program (DPP) Research Group,
Miriam S. Udler[1,2,3,4], Aaron Leong[1,2,3,4,6], Josep M. Mercader[1,2,3,4], Jose C. Florez[1,2,3,4]

Diabetologia. 2023 July ; 66(7): 1260–1272. doi:10.1007/s00125-023-05922-7.

- Challenged 1000 patients with metformin and glipizide
- Examined almost 1000 genetic sites associated with diabetes development or glycemic traits
- Genome-wide analysis identified 5 novel variants associated with greater responses to metformin (3) and glipizide (2)

Identification of Genotypes Associated with Metformin Response





- Reduced response to metformin
- In DPP, associated with higher HbA1c over time

SUGAR-MGH

More Genetic Data on Risk for Developing T2D

HOME | NEWS

Study reveals genetic clusters that may explain differences in type 2 diabetes risk

The clusters point to a range of biological processes that likely contribute to the development of type 2 diabetes.

By Brandon Chase, Massachusetts General Hospital Communications

March 8, 2024

•Nature Medicine Published: 05 March 2024

More Sensible Approaches to Precision Medicine

1. Recognize and identify heterogeneity of “Type 2 diabetes”
   Subtypes by:
   a) Genetics
   b) Demographics
   c) Phenotyping
      i. Pathophysiology
      ii. Outcomes
   d) AI approaches

Challenges: Even if understanding the relationship between genotypes and diabetes sub-types and potential response to specific medications is progressing, genotyping is far from widely available.

2. Apply interventions across different subtypes to determine whether different therapies have differential effects across sub-types.

More Sensible Approaches to Precision Medicine

1. Recognize and identify heterogeneity of "Type 2 diabetes" Subtypes by:
   a) Genetics
   b) Demographics
   c) Phenotyping
      i. Pathophysiology
      ii. Outcomes
   d) AI approaches
2. Apply interventions across different subtypes to determine whether different therapies have differential effects across sub-types.

Challenges: Most trials have historically not been diverse enough to provide adequate power across racial/ethnic/sex groups.

More Sensible Approaches to Precision Medicine

Lack of Diversity in Diabetes Trials- NEJM 2021-24

	Medications	Study Pop #	Demographics (% Race) White	Black	Asian	AI/AN
Wharton	GLP	272	94	6	0	0
Rosenstock (ONWARDS)	Icodec	984	67	4	28	11
Harrington (EMPA KIDNEY)	Empagliflozin	6,609	59	4	36	
Bhatt (SOLOIST-WHF)	Sotogliflozin	1222	93	4	1	
Bhatt (SCORED)	Sotogliflozin	10,584	83	3	6	4
Frias (SURPASS 2)	Tirzepatide	1879	83	4	1	11
Solomon (DELIVER)	Dapagliflozin	6263	71	3	20	
Arslanian (AWARD-Peds)	Dulaglutide	154	55	15	12	10
Gerstein (AMPLITUDE O)	Efpeglenatide	4076	87			
Pitt (FIGARO-DKD)	Finerone	7437	72	3	20	
Total		**40,857**	**33061 (81%)**	**2185 (5%)**	**6231(15%)**	**854(2%)**

Remarkably (unfortunately) Little Data on Responsiveness to Therapies Based on Easily Available Demographic, Social and other Data

Of the 11 high-quality, high-profile intervention studies in T2DM published in NEJM during the past three years:

- None of the pharma-sponsored studies included a diverse enough population to examine subgroups defined by race
- Only the NIH-sponsored GRADE study- the comparative effectiveness study of insulin glargine, the GLP liraglutide, sulfonylurea glimepiride and DPP-4 inhibitor included a diverse enough population to attempt sub-group analyses.

More Sensible Approaches to Precision Medicine

1. Recognize and identify heterogeneity of "Type 2 diabetes" Subtypes by:
   a) Genetics
   b) Demographics
   c) Phenotyping
      i. Pathophysiology
      ii. Outcomes
   d) AI approaches
2. Apply interventions across different subtypes to determine whether different therapies have differential effects across sub-types.

For example: classify T2D on the basis of secretory defects vs resistance.

Challenge: beyond limited data, phenotyping not easily/clinically available or affordable at this time.

More Sensible Approaches to Precision Medicine

1. Recognize and identify heterogeneity of “Type 2 diabetes” Subtypes by:
   a) Genetics
   b) Demographics
   c) Phenotyping
      i. Pathophysiology
      ii. Outcomes
   d) AI approaches
2. Apply interventions across different subtypes to determine whether different therapies have differential effects across sub-types.

Diverse Study

GRAD ing
medic

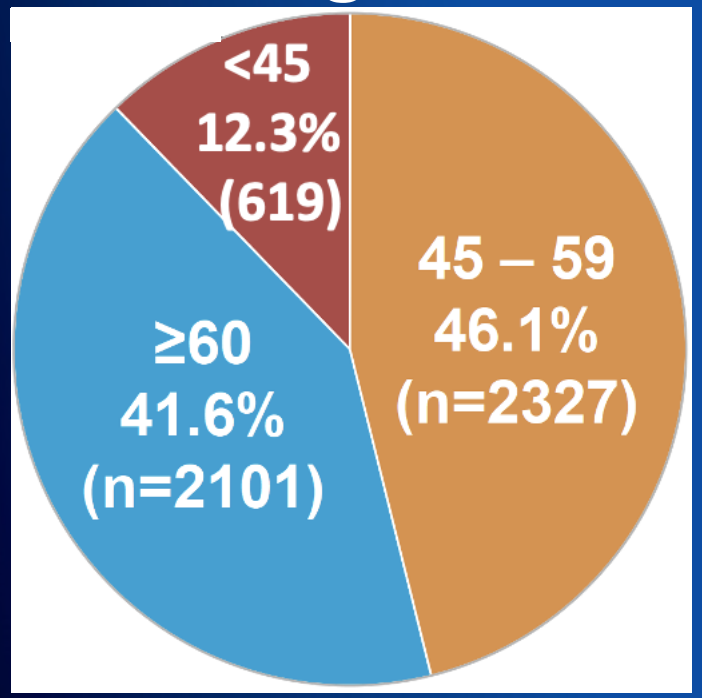
- Stu
- Ad

Aimed to recruit a diverse population, mirroring the population with type 2 diabetes in the United States.

GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

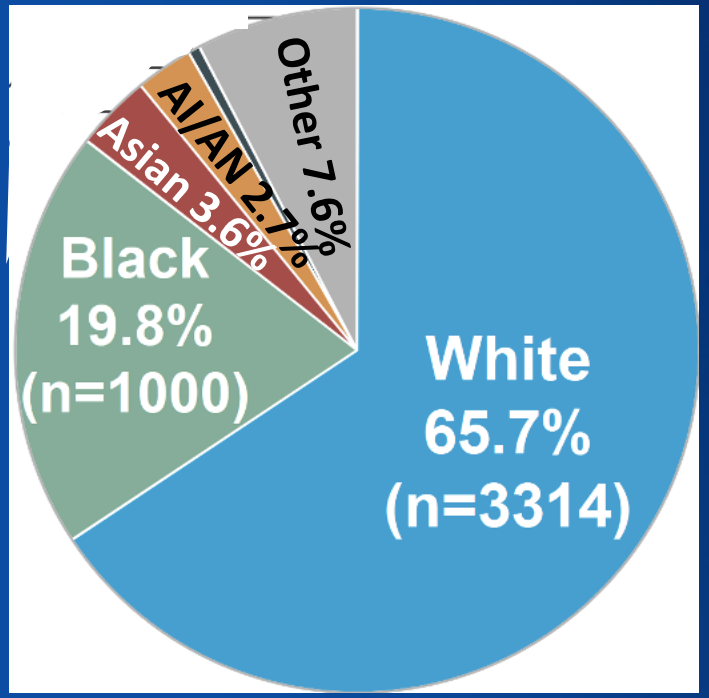
Diverse Study

Age



Mean 57 ± 10 y

Race



Ethnicity

GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Sub-group Analyses

Pre-defined Sub-groups

We conducted separate subgroup analyses for race (White, Black, and all Others) and for ethnicity (Hispanic versus Non-Hispanic).

To date, no differences in response to therapies based on demography.

HbA1c was the only heterogeneous factor as defined by tertiles (6.8-7.2%, 7.3-7.7%, 7.8-8.5%)

Ongoing analyses to examine whether genetic factors or physiologic factors moderate responses to therapies.

GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Precision (or Personalized) Medicine

CONSENSUS REPORT

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Diabetologia 2020; 63:1671

Precision diabetes medicine has found a firm foothold in the diagnosis and treatment of monogenic diabetes, while the application of precision medicine to other types of diabetes is at this time aspirational, rather than standard of care.

Precision (or Personalized) Medicine

Genetic drivers of heterogeneity in type 2 diabetes pathophysiology

Nature | Vol 627 | 14 March 2024 | 347

This might offer a route to optimize global access to genetically informed diabetes care.

Precision (or Personalized) Medicine

Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine

Nat Med. 2023 October ; 29(10): 2438–2457

The key findings of this second consensus report are that, within the areas examined, several

A key finding of this consensus report is that trials explicitly designed to test precision

m **Precision diabetes medicine is currently largely aspirational.** s.

precision medicine hypotheses. There is also a dearth of relevant, high-quality research in people of non-European ancestry, hindering the development and implementation of precision diabetes medicine in many of the most heavily burdened populations worldwide.