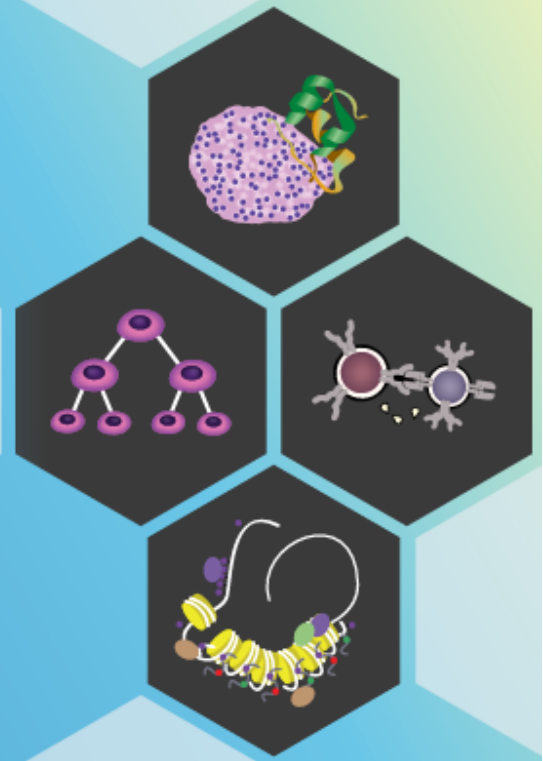
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Debate: Precision Medicine in Type 2 Diabetes: We Are Really Close



Paul W. Franks, PhD

Professor, Department of Clinical Sciences

Lund University, Sweden

Disclosures

- Consultant for Novo Nordisk A/S, and Zoe Global Ltd.
- Grant/Research Support (paid to my institution) from multiple pharmaceutical companies via the Innovative Medicines Initiative of the European Union.

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

The off-label/investigational use of Metformin, Sulfonylureas, and Incretin pathway drugs will be addressed.

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.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

What precisely do we mean by "precision medicine"?

Precision medicine:

"*Precision medicine focuses on **minimizing errors and improving accuracy** in medical decisions and health recommendations. It seeks to maximize efficacy, cost-effectiveness, safety, access for those in need and compliance compared with contemporary evidence-based medicine. Precision medicine emphasizes tailoring diagnostics or therapeutics (prevention or treatment) to subgroups of populations sharing similar characteristics.*"

Personalized medicine:

"*The use of a person's own data to **objectively** gauge the efficacy, safety, and tolerability of therapeutics, and, **subjectively**, to tailor health recommendations and/or medical decisions to the individual's preferences, circumstances, and capabilities.*"

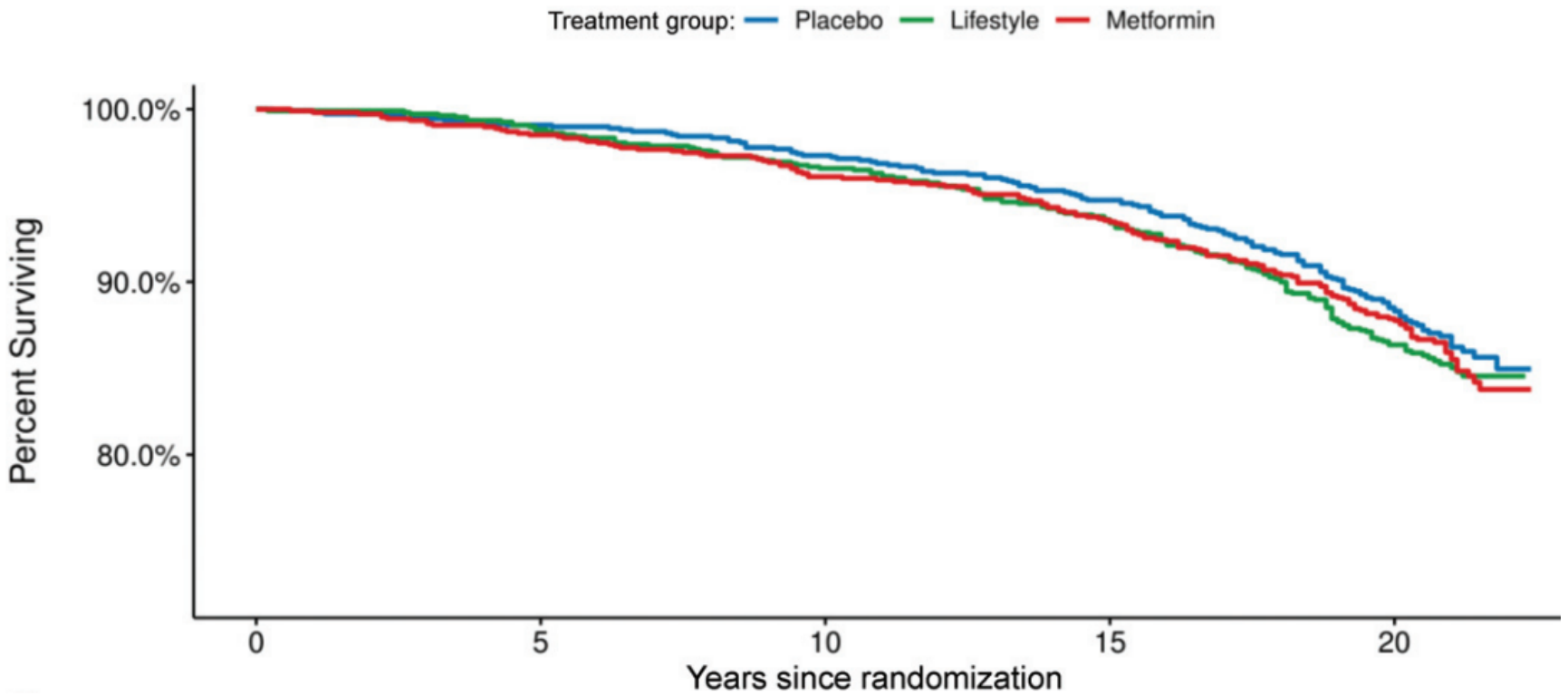
Tobias D, *et al*. | *Nature Medicine* | 2023. 29(10): 2438–2457.

Common misconceptions:

1. **Current approaches work just fine**
2. **Precision medicine is what doctors have always done**
3. **Precision medicine is all about genetics & drugs**

#1: Current approaches work just fine:

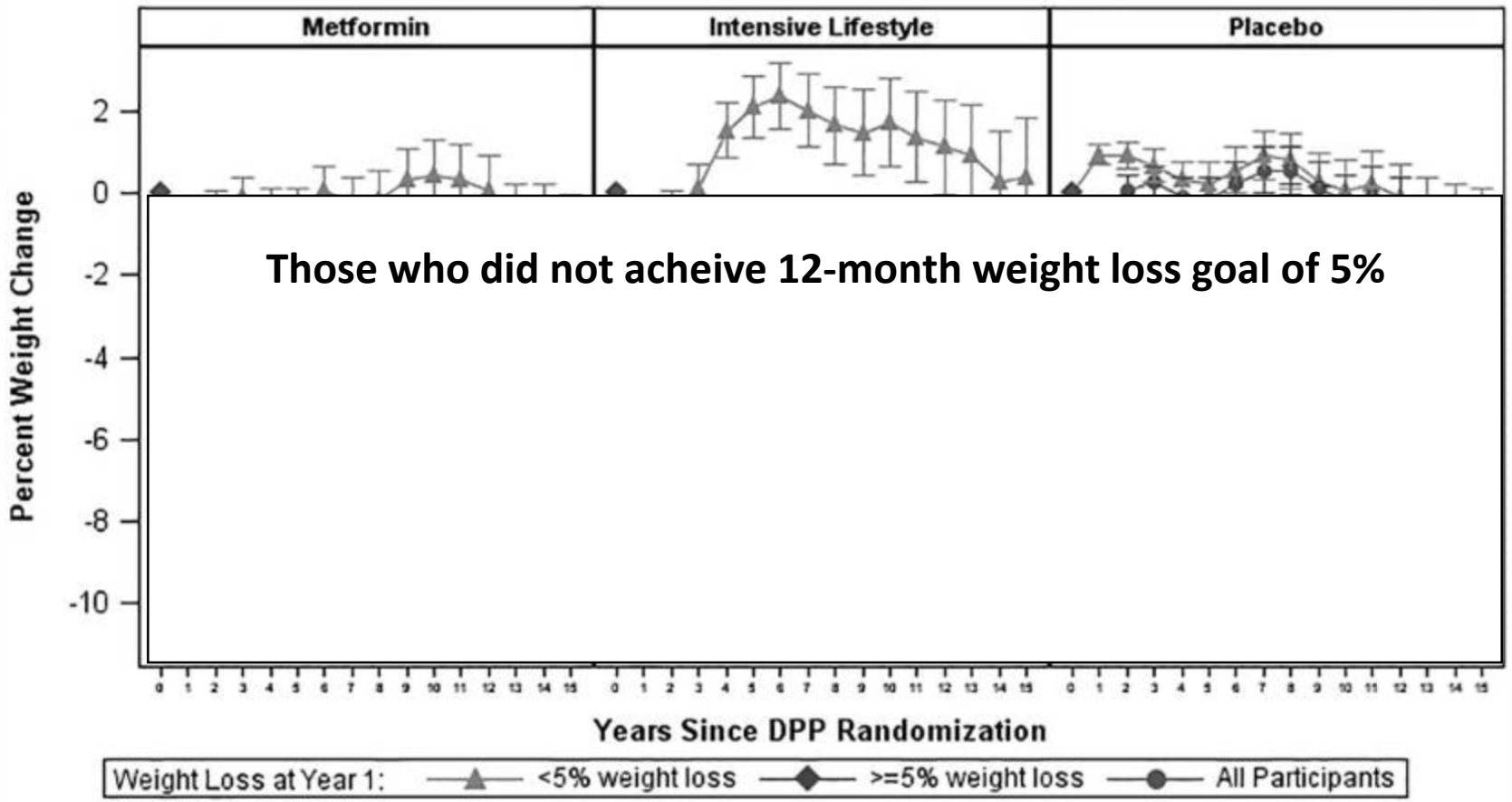
Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study



Lee CG, *et al.* | *Diab. Care.* | 2021. 44(12):2775-2782.

#1: Current approaches work just fine:

Long-Term Weight Loss With Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study



Apolzan JW, *et al*. | *Ann Int Med.* | 2019. 170(10):682-690.

#1: Current approaches work just fine:

Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes

The New England
Journal of Medicine

VOLUME 346 FEBRUARY 7, 2002 NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

ABSTRACT

Background Type 2 diabetes affects approximately 8 percent of adults in the United States. Some risk factors — elevated plasma glucose concentrations in the fasting state and after an oral glucose load, overweight, and a sedentary lifestyle — are potentially reversible. We hypothesized that modifying these factors with a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes.

Methods We randomly assigned 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week. The mean age of the participants was 51 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 34.0; 68 percent were women, and 45 percent were members of minority groups.

Results The average follow-up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence by 58 percent (95 percent confidence interval, 48 to 66 percent) and metformin by 31 percent (95 percent confidence interval, 17 to 43 percent), as compared with placebo; the lifestyle intervention was significantly more effective than metformin. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle-intervention program, and 13.9 would have to receive metformin.

Conclusions Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin. (N Engl J Med 2002; 346:393-403.)

TYPE 2 diabetes mellitus, formerly called non-insulin-dependent diabetes mellitus, is a serious, costly disease affecting approximately 8 percent of adults in the United States.[1] Treatment prevents some of its devastating complications[2,3] but does not usually restore normoglycemia or eliminate all the adverse consequences. The diagnosis is often delayed until complications are present.[4] Since current methods of treating diabetes remain inadequate, prevention is preferable. The hypothesis that type 2 diabetes is preventable[5,6] is supported by observational studies and two clinical trials of diet, exercise, or both in persons at high risk for the disease[7,8] but not by studies of drugs used to treat diabetes.[5]

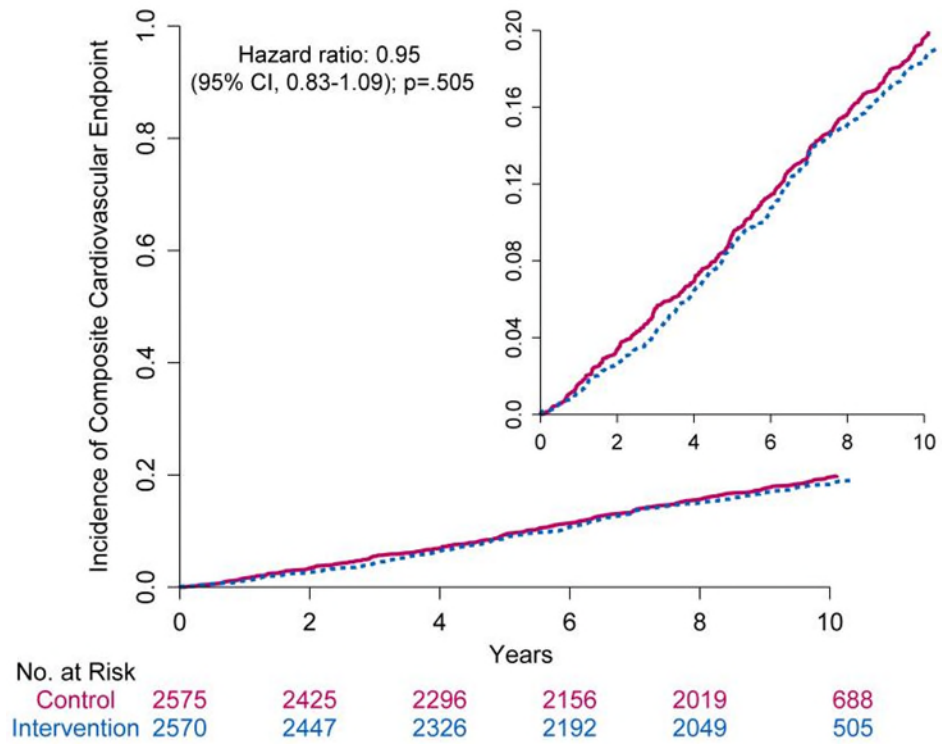
The validity of generalizing the results of previous prevention studies is uncertain.[9] Interventions that work in some societies may not work in others, because social, economic, and cultural forces influence diet and exercise. This is a special concern in the United States, where there is great regional and ethnic diversity in lifestyle patterns and where diabetes is especially frequent in certain racial and ethnic groups, including American Indians, Hispanics, African Americans, Asians, and Pacific Islanders.[10]

The Diabetes Prevention Program Research Group conducted a large, randomized clinical trial involving adults in the United States who were at high risk for the development of type 2 diabetes. The study was designed to answer the following primary questions: Does a lifestyle intervention or treatment with

The writing group (William C. Knowler, M.D., Dr.P.H., Elizabeth Barrett-Connor, M.D., Sarah E. Fowler, Ph.D., Richard F. Hamman, M.D., Dr.P.H., John M. Lachin, Sc.D., Elizabeth A. Walker, D.N.Sc., and David M. Nathan, M.D.) takes responsibility for the content of this article.

Address reprint requests to the Diabetes Prevention Program Coordinating Center, Biostatistics Center, George Washington University, 6110 Executive Blvd., Suite 750, Rockville, MD 20852.

*The members of the Diabetes Prevention Program Research Group are listed in the Appendix.

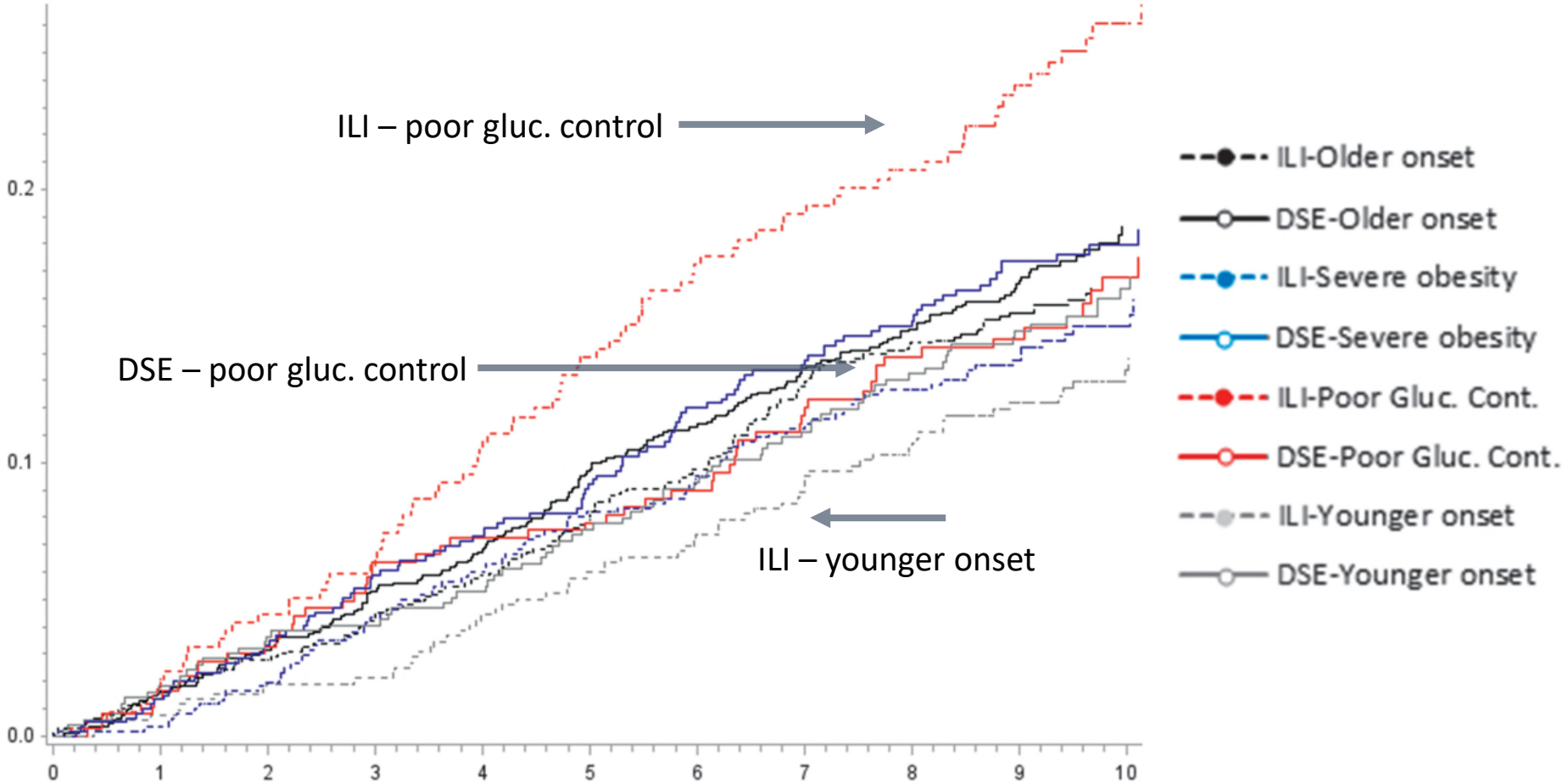


Wing RR, *et al.* | *N Engl J Med.* | 2013. 369(2):145-54.

#1: Current approaches work just fine:

Type 2 Diabetes Subgroups, Risk for Complications, and Differential Effects Due to an Intensive Lifestyle Intervention

Cumulative hazards of CVD



Bancks M.P., *et al.* | *Diab. Care.* | 2021. 44(5):1203-1210.

#2: Precision medicine is what doctors have always done

High-Risk and Population Strategies of Prevention: Ethical Considerations

Geoffrey Rose

(Annals of Medicine 21: 409—413, 1989)

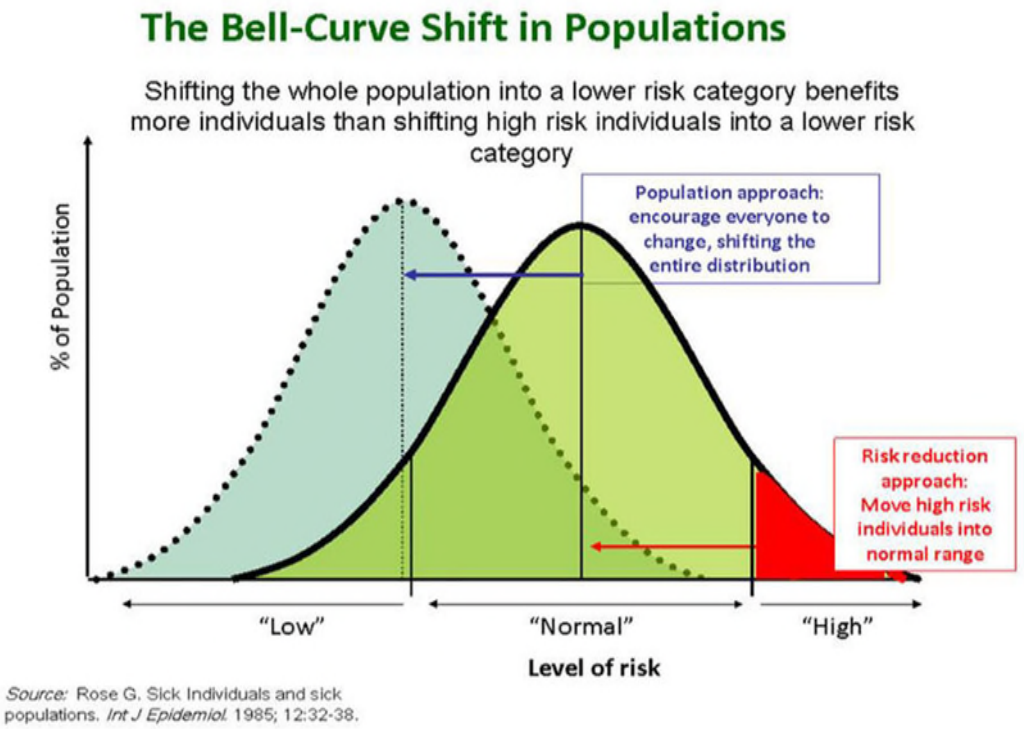
The Individual or High-Risk Approach

Medicine is traditionally concerned with the health problems of individuals (1). Applied to prevention this means that we seek to identify individuals who are liable to develop illness, and then help them to obtain protection or to take avoiding action. We look for correctable risk factors in coronary-prone individuals, or for hypertension as a lead to preventing strokes, or for signs of susceptibility to dental caries, rhesus haemolytic disease, rubella and so on. For doctors this is the natural and acceptable way into prevention, for it is a small step from accepting responsibility for today's sick to accepting responsibility for tomorrow's sick; and, once identified, these high-risk individuals can be managed within the medical care system, just as though they were patients. It is the medical model of prevention (but not to be condemned on that account).

Underlying Assumptions

The approach implies the possibility of dividing people into two groups — the disease-prone deviants, and the healthy (normal) remainder. This neat classification turns out to be a considerable oversimplification, firstly because susceptibility is rarely confined to a distinct high-risk minority, and secondly because although we can differentiate high- and low-risk groups, our ability to predict the future for individuals is weak. On the one hand, five out of six heavy smokers do *not* get lung cancer. On the other hand, in those men in our Whitehall Study who fell into the lowest 10 % of estimated coronary risk, the single commonest cause of death was still coronary heart disease! Errors are common in both directions.

#2: Precision medicine is what doctors have always done



Source: Rose G. Sick Individuals and sick populations. *Int J Epidemiol.* 1985; 12:32-38.

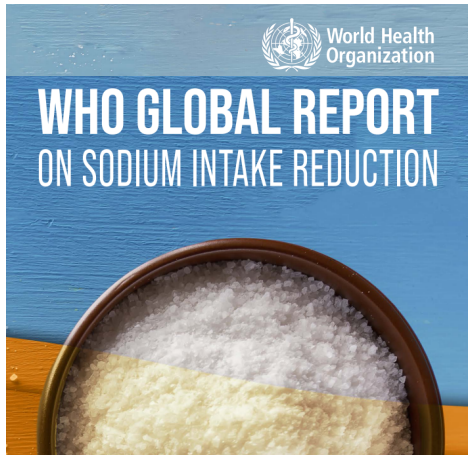


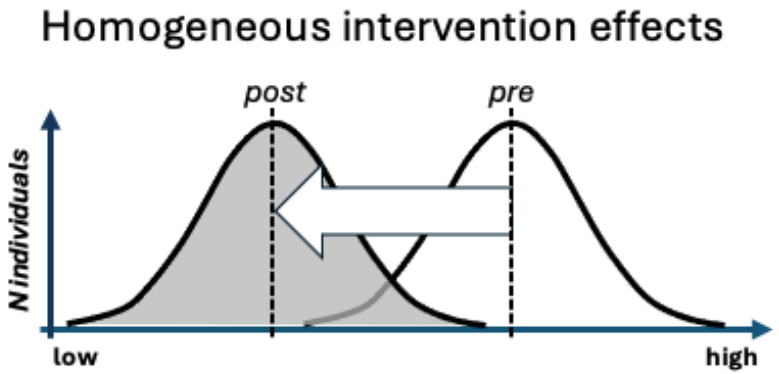
Table 9. Number and proportion of cardiovascular deaths averted by WHO region, at year 2025 and 2030

WHO region	2025		2030	
	Cardiovascular aggregated deaths averted (millions)	%	Cardiovascular aggregated deaths averted (millions)	%
Africa	0.087	1.3	0.278	2.3
Americas	0.199	1.4	0.628	2.5
Eastern Mediterranean	0.086	0.9	0.275	1.6
European	0.293	1.1	0.903	1.9
South-East Asia	0.507	1.8	1.620	3.1
Western Pacific	1.022	2.5	3.242	4.4
Global	2.194	1.7	6.946	3.1

Thirteen Member States: Andorra, Cook Islands, Democratic People's Republic of Korea, Democratic Republic of the Congo, Dominica, Marshall Islands, Monaco, Nauru, Niue, Palau, Saint Lucia, San Marino and Tuvalu did not have all the parameters available to compute the corresponding cardiovascular deaths averted. Three Member States: Czechia, Lithuania and Saudi Arabia were already in the maximum level of the score 4 so did not benefit from the uplifted scenario.

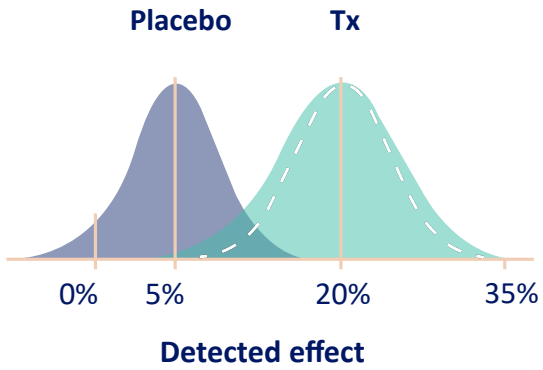
#2: Precision medicine is what doctors have always done

Population strategy

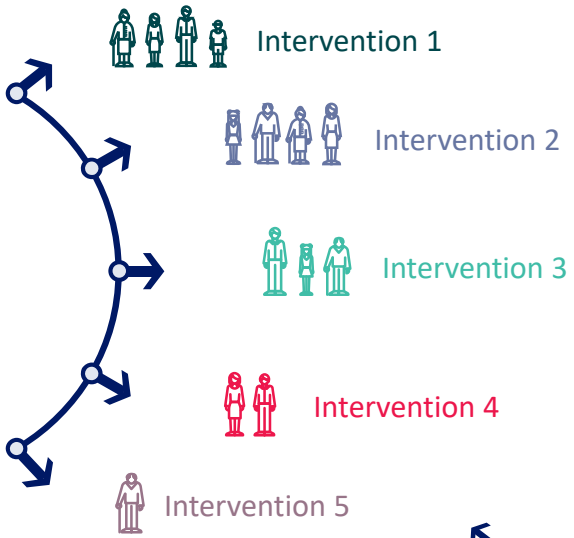


#2: Precision medicine is what doctors have always done

1. Evidence-based medicine
Estimate average risk/response using epidemiological and clinical trial cohorts

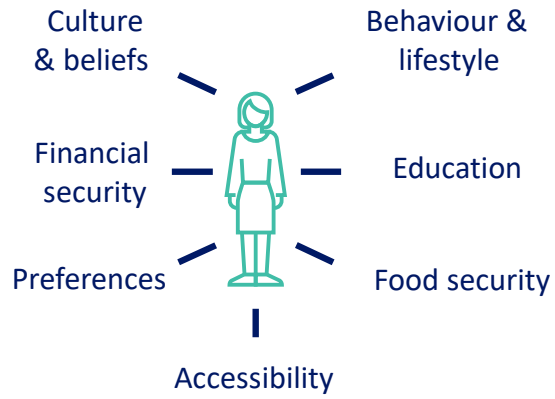


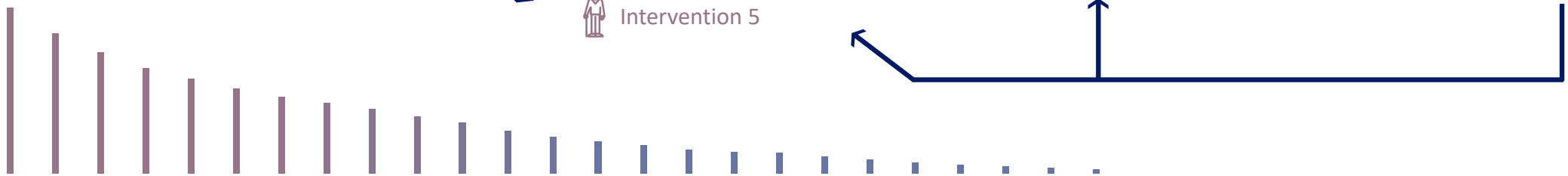
2. Probability scoring/stratification
Maximize response/minimise risk using subclassification



3. Personalisation (objective)
Monitor response to optimise dose, timing, delivery

4. Personalisation (subjective)
Adapt intervention to fit the person's needs, capabilities, preferences





High error/low accuracy

Low error/high accuracy

Franks P.W., et al. | *Lancet Diab & Endo.* | 2023; (11):822-835

#3: Precision medicine is all about genetics and drugs

nature medicine

Explore content | About the journal | Publish with us | Subscribe

nature > nature medicine > articles > article

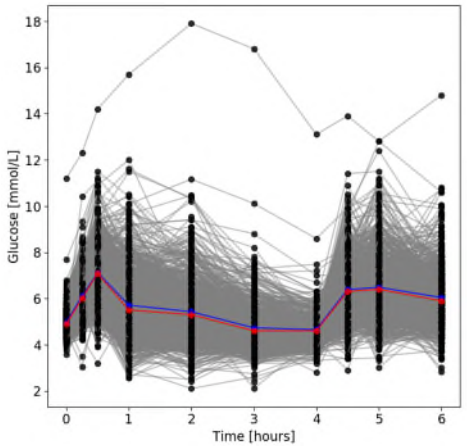
Article | Published: 05 March 2024

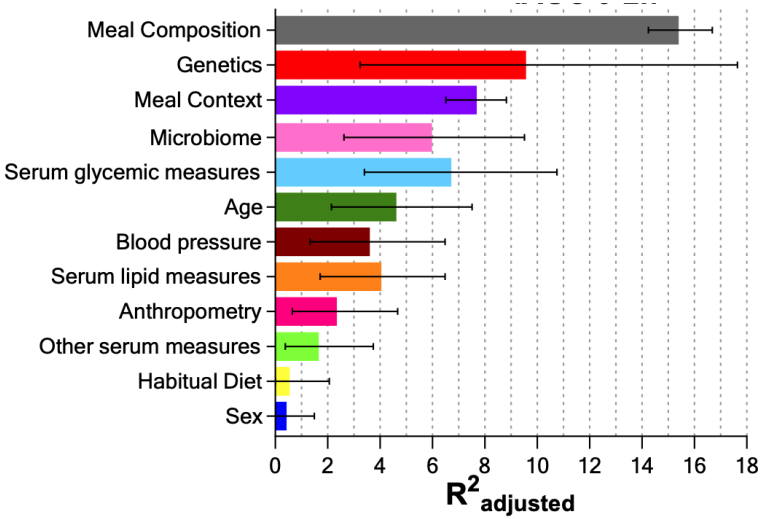
Multi-ancestry polygenic mechanisms of type 2 diabetes

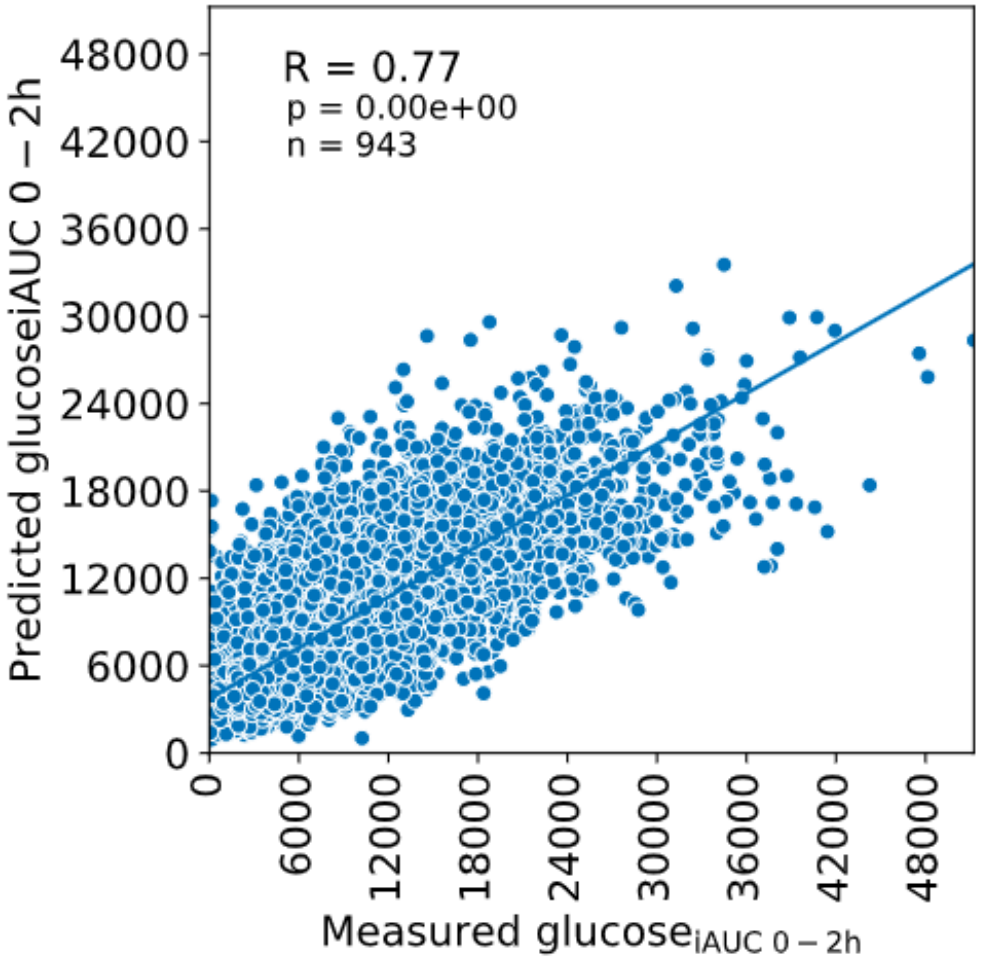
Kirk Smith, Aaron J. Deutsch, Carolyn McGrail, Hyunkyung Kim, Sarah Hsu, Alicia Huerta-Chagoya, Ravi Mandla, Philip H. Schroeder, Kenneth E. Westerman, Lukasz Szczerbinski, Timothy D. Majarian, Varinderpal Kaur, Alice Williamson, Noah Zaitlen, Melina Claussnitzer, Jose C. Florez, Alisa K. Manning, Josep M. Mercader, Kyle J. Gaulton & Miriam S. Udler

Nature Medicine **30**, 1065–1074 (2024) | Cite this article

#3: Precision medicine is all about genetics and drugs



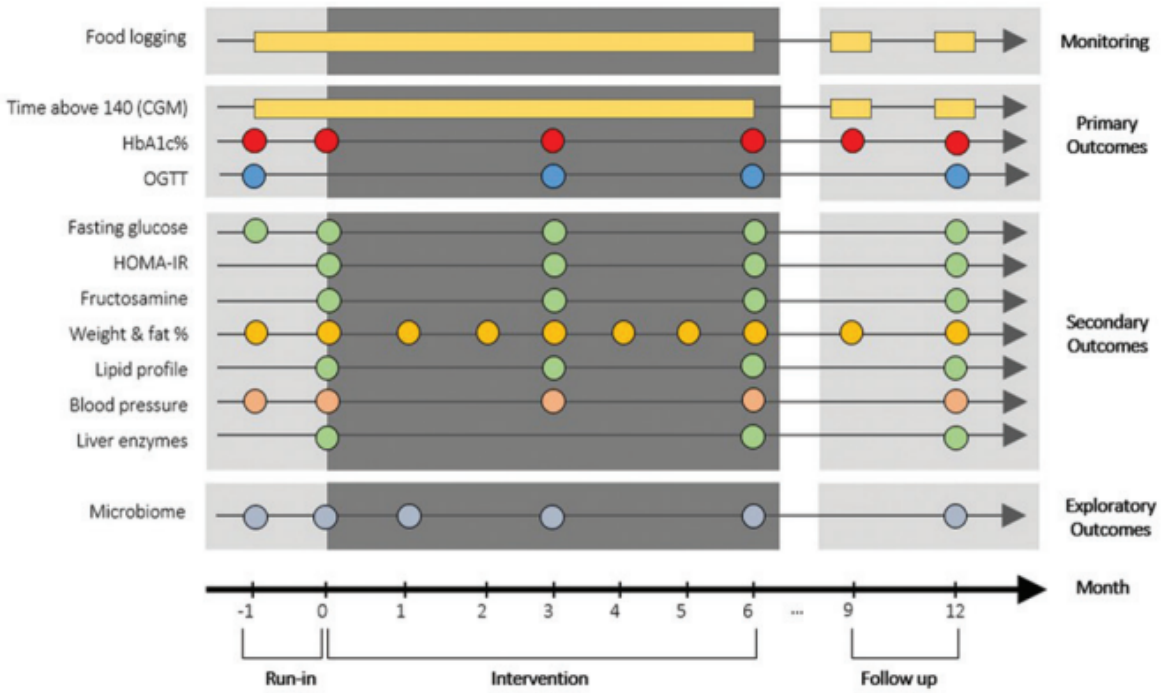


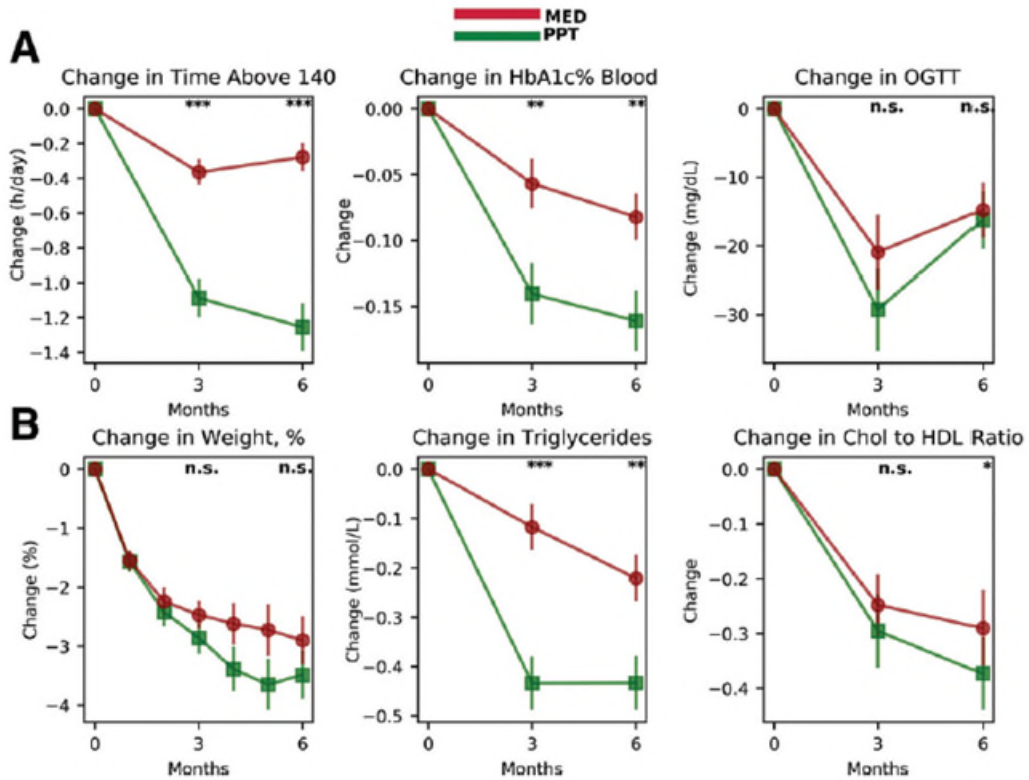


Berry S. et al. | *Nat Med*. | 2020; 26(6):964-973

#3: Precision medicine is all about genetics and drugs

Machine learning-determined personalised nutrition in type 2 diabetes



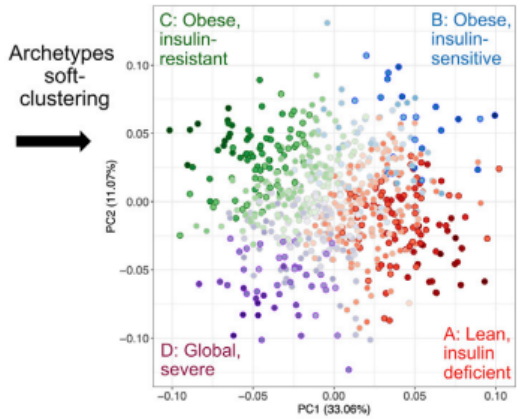


Ben-Yacov O., et al. | *Diabetes Care*. | 2021;44(9):1980-1991

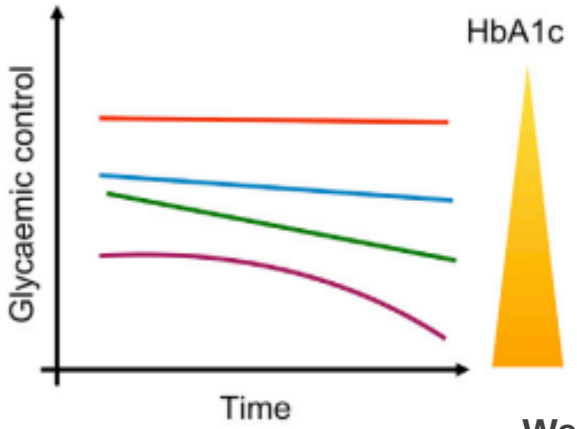
#3: Precision medicine is all about genetics and drugs

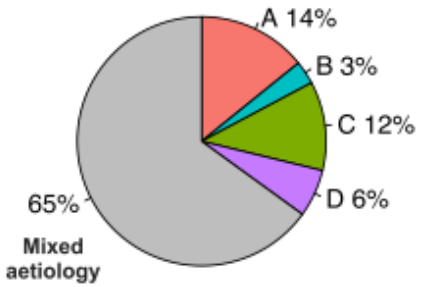
Machine learning-determined subclassifications in type 2 diabetes

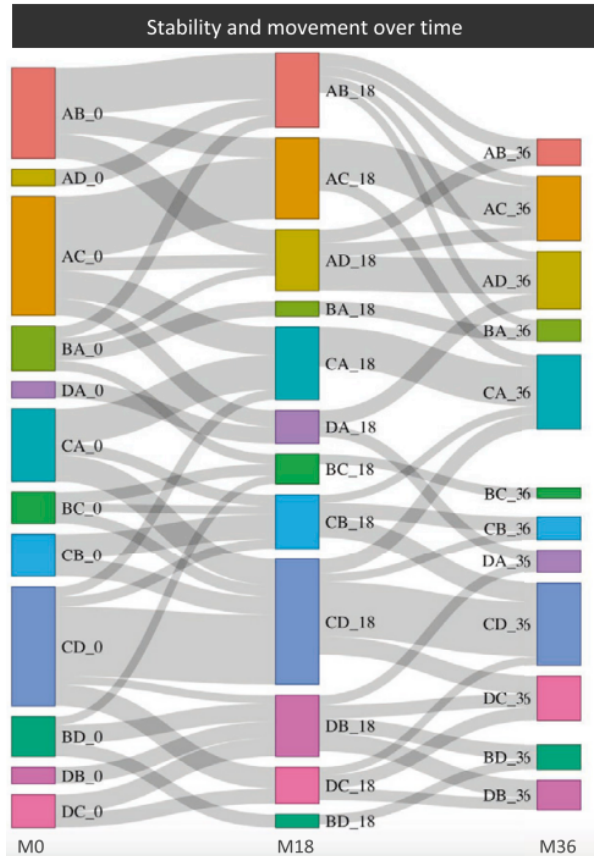
- Soft clustering based on 32 phenotypes identified 4 quantitative archetypes
- These reflect different patterns of dysfunction across T2D etiological processes
- The four archetypes are different in disease progression, GRSs, and omics signals



Four stable archetypes of T2D show differences in disease progression, circulating omics biomarkers and genetic risk scores







Wesolowska-Andersen A., et al. | *Cell Rep Med.* | 2022;3(1):100477

#3: Precision medicine is all about genetics & drugs

Patient stratification for determining optimal second-line and third-line therapy for type 2 diabetes: the TriMaster study

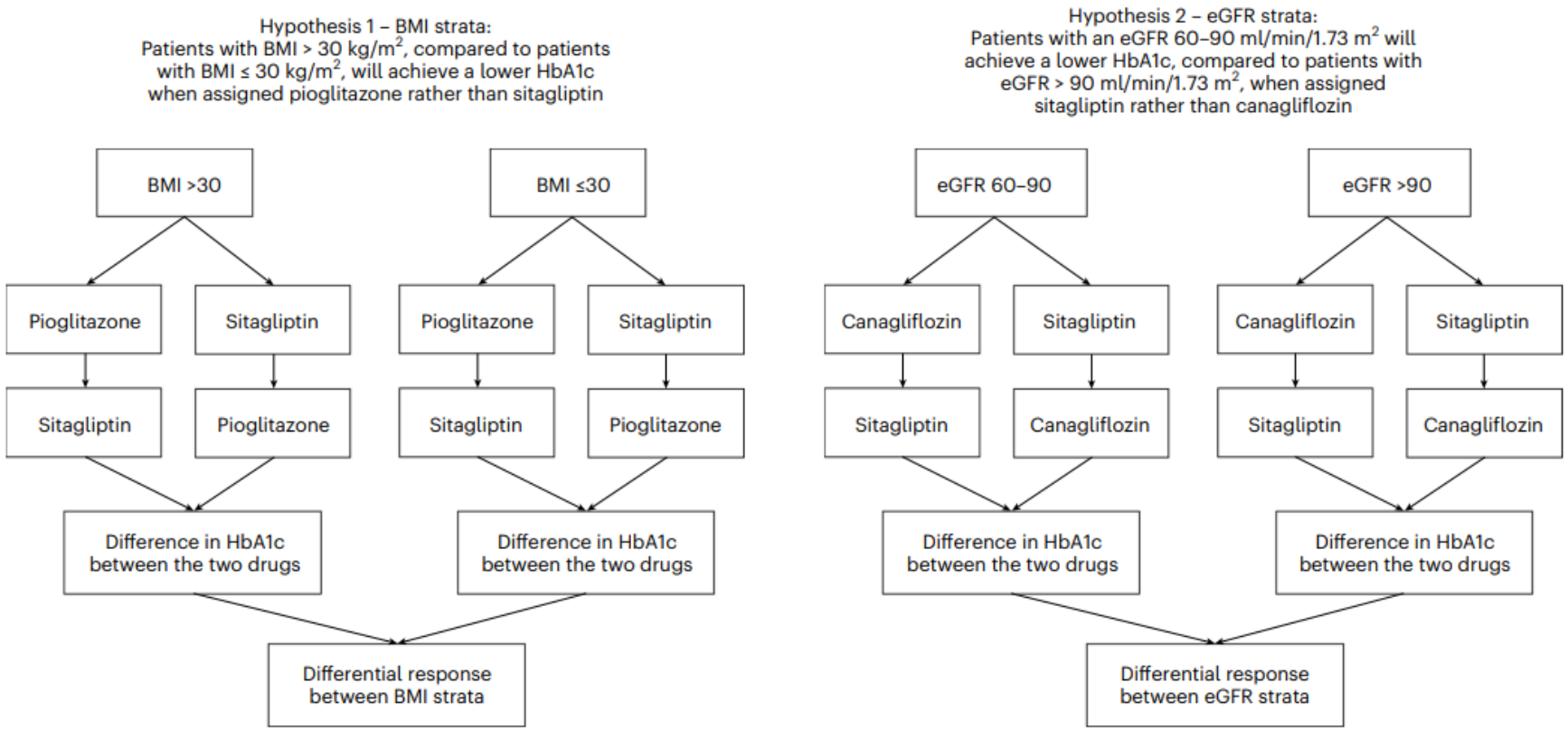


Fig. 2 | The two main hypotheses being tested in TriMaster. Flow diagram showing the comparisons and outcomes for each of the hypotheses: differential response to pioglitazone and sitagliptin between BMI strata, and differential response to sitagliptin and canagliflozin between eGFR strata.

Shields B., et al. | *Nat Med.* | 2023;29(2):376-383.

nature medicine

Consensus Statement

https://doi.org/10.1038/s41591-023-02502-5

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

Received: 17 May 2023

Accepted: 14 July 2023

Published online: 5 October 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Precision medicine is part of the logical evolution of contemporary evidence-based medicine that seeks to reduce errors and optimize outcomes when making medical decisions and health recommendations. Diabetes affects hundreds of millions of people worldwide, many of whom will develop life-threatening complications and die prematurely. Precision medicine can potentially address this enormous problem by accounting for heterogeneity in the etiology, clinical presentation and pathogenesis of common forms of diabetes and risks of complications. This second international consensus report on precision diabetes medicine summarizes the findings from a systematic evidence review across the key pillars of precision medicine (prevention, diagnosis, treatment, prognosis) in four recognized forms of diabetes (monogenic, gestational, type 1, type 2). These reviews address key questions about the translation of precision medicine research into practice. Although not complete, owing to the vast literature on this topic, they revealed opportunities for the immediate or near-term clinical implementation of precision diabetes medicine; furthermore, we expose important gaps in knowledge, focusing on the need to obtain new clinically relevant evidence. Gaps include the need for common standards for clinical readiness, including consideration of cost-effectiveness, health equity, predictive accuracy, liability and accessibility. Key milestones are outlined for the broad clinical implementation of precision diabetes medicine.

Diabetes is a major global problem, with many hundreds of millions of people affected by the disease, many of whom are undiagnosed. The major burden of diabetes is exerted through the development of life-threatening complications, often involving damage to large and small blood vessels. The disease is currently classified into several types of diabetes. The two most common forms are type 1 diabetes (T1D), an autoimmune disease accounting for ~2% of all forms of diabetes worldwide[1], and type 2 diabetes (T2D), which accounts for most of the remaining cases. Rare 'monogenic' forms of diabetes also exist, with gestational diabetes mellitus (GDM) being an additional category (Box 1). A major challenge with most diabetes is that it is heterogeneous in etiology, clinical presentation and prognosis. Understanding and leveraging this heterogeneity is a core objective of precision diabetes medicine (Fig. 1).

This second international consensus report from the Precision Medicine in Diabetes Initiative (PMDI) summarizes the comprehensive systematic reviews and resulting consensus among the PMDI consortium for the pillars of precision medicine prevention, diagnosis, treatment and prognosis[2] across monogenic diabetes mellitus (MDM), GDM, T1D and T2D[3–16] (Fig. 2). The objectives of the PMDI consortium were to identify (1) where current evidence supports the application of precision approaches in diabetes prevention and care, and (2) key gaps where additional and/or higher quality evidence is needed before precision medicine can be implemented. Areas of consensus for these

e-mail: paul.franks@med.lu.se

nature medicine

Consensus Statement

https://doi.org/10.1038/s41591-024-03033-3

Reporting guidelines for precision medicine research of clinical relevance: the BePRECISE checklist

Received: 21 March 2024

Accepted: 29 April 2024

Published online: 19 July 2024

Check for updates

A list of authors and their affiliations appears at the end of the paper

Precision medicine should aspire to reduce error and improve accuracy in medical and health recommendations by comparison with contemporary practice, while maintaining safety and cost-effectiveness. The etiology, clinical manifestation and prognosis of diseases such as obesity, diabetes, cardiovascular disease, kidney disease and fatty liver disease are heterogeneous. Without standardized reporting, this heterogeneity, combined with the diversity of research tools used in precision medicine studies, makes comparisons across studies and implementation of the findings challenging. Specific recommendations for reporting precision medicine research do not currently exist. The BePRECISE (Better Precision-data Reporting of Evidence from Clinical Intervention Studies & Epidemiology) consortium, comprising 23 experts in precision medicine, cardiometabolic diseases, statistics, editorial and lived experience, conducted a scoping review and participated in a modified Delphi and nominal group technique process to develop guidelines for reporting precision medicine research. The BePRECISE checklist comprises 23 items organized into 5 sections that align with typical sections of a scientific publication. A specific section about health equity serves to encourage precision medicine research to be inclusive of individuals and communities that are traditionally under-represented in clinical research and/or underserved by health systems. Adoption of BePRECISE by investigators, reviewers and editors will facilitate and accelerate equitable clinical implementation of precision medicine.

Precision medicine represents an evolution in the long history of evidence-based medicine and healthcare. Spanning disease classifications and risk factor boundaries, precision medicine is underpinned by four key 'pillars' (prevention, diagnosis, treatment and prognosis)[1,2]. The overarching objective of precision medicine is to reduce error and improve accuracy in medical and health recommendations compared with contemporary approaches[3]. Precision medicine solutions should meet or improve on existing standards for safety. They should also be compatible with the individual's preferences, capabilities and needs and tailored to the cultural and societal conditions of the population. Furthermore, precision medicine should be cost-effective and enhance health equity by increasing access to better medical and healthcare practices for the people most in need.

Cardiometabolic diseases are the leading causes of mortality globally[4]. With this burden projected to worsen over the coming decades[5], innovative approaches to disease prevention, diagnosis and treatment are urgently needed. A plethora of precision medicine approaches are being explored in translational and clinical research.

e-mail: paul.franks@med.lu.se

Summary:

1. **Precision medicine can help overcome some major weaknesses of contemporary medicine:**
    - Requires trial and error
    - Can be costly
    - Can enhance health inequities…
    - …leaves some of those most in need behind
2. **Precision medicine does not have to be expensive, nor require cutting-edge technologies**
3. **There are now many examples of precision diabetes medicine that are ready for clinical translation, and frameworks in place to implement them.**