What can we learn from precision medicine in diabetes?

Paris NASH meeting – Sept 8th, 2023

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Co-chair, ADA/EASD Precision Medicine in Diabetes Initiative
Co-chair, Working Group of Council - NIDDK Heterogeneity of Diabetes Initiative

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ADA/EASD Precision Medicine in Diabetes Initiative

Diabetes Care Volume 43, July 2020 1617

Precision Medicine in Diabetes: A Consensus Report From the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care 2020;43:1617–1635 | https://doi.org/10.2337/dci20-0022

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CONSENSUS REPORT

The convergence of advances in medical science, human biology, data science, and technology has enabled the generation of new insights into the phenotype known as "diabetes." Increased knowledge of this condition has emerged from populations around the world, illuminating the differences in how diabetes presents, its variable prevalence, and how best practice in treatment varies between populations. In parallel, focus has been placed on the development of tools for the application of precision medicine to numerous conditions. This Consensus Report presents the American Diabetes Association (ADA) Precision Medicine in Diabetes Initiative in partnership with the European Association for the Study of Diabetes (EASD), including its mission, the current state of the field, and prospects for the future. Expert opinions are presented on areas of precision diagnostics and precision therapeutics (including prevention and treatment), and key barriers to and opportunities for implementation of precision diabetes medicine, with better care and outcomes around the globe, are highlighted. Cases where precision diagnosis is already feasible and effective (i.e., monogenic forms of diabetes) are presented, while the major hurdles to the global implementation of precision diagnosis of complex forms of diabetes are discussed. The situation is similar for precision therapeutics, in which the appropriate therapy will often change over time owing to the manner in which diabetes evolves within individual patients. This Consensus Report describes a foundation for precision diabetes medicine, while highlighting what remains to be done to realize its potential. This, combined with a subsequent, detailed evidence-based review (due 2022), will provide a roadmap for precision medicine in diabetes that helps improve the quality of life for all those with diabetes.

RATIONALE FOR PRECISION MEDICINE IN DIABETES

The practice of medicine centers on the individual. From the beginning, the physician has examined the patient suffering from illness, ascertained his/her signs and symptoms, related them to the medical knowledge available at the time, recognized patterns that fit a certain category and, based on the practical wisdom accumulated via empirical trial and error, applied a given remedy that is best suited to the situation at hand. Thus, the concept of *precision medicine*, often defined as

- Common terminology/definitions
- Frame-work (pillars):
  - Prevention
  - Diagnosis
  - Treatment
  - Prediction/prognosis
- Expert opinion
- Road-map (inc. systematic evidence reviews)

ADA/EASD Precision Medicine in Diabetes Initiative

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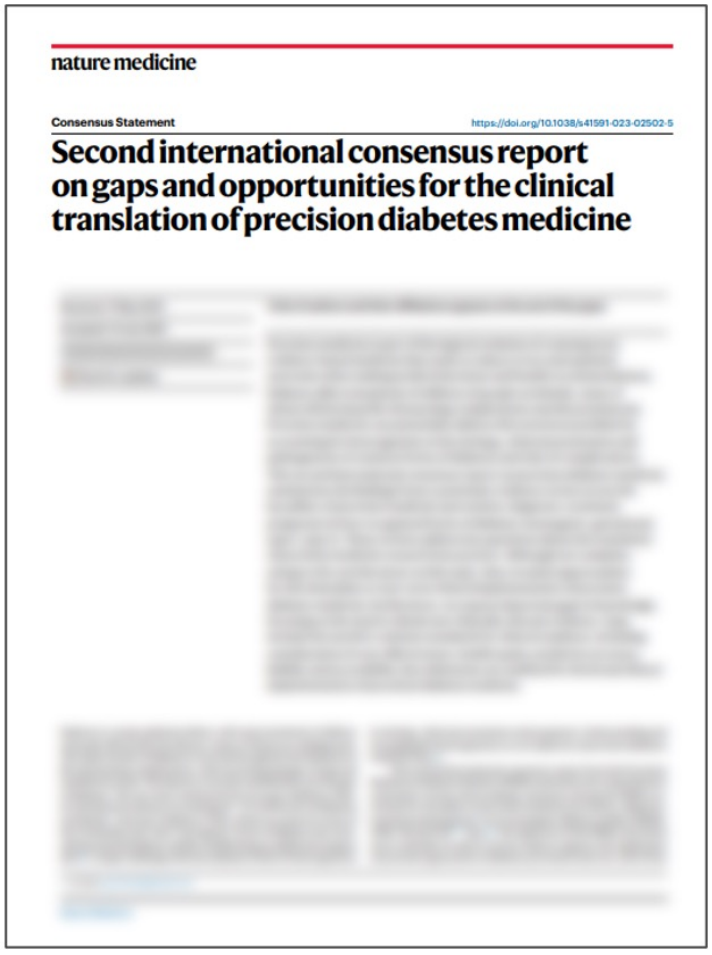
CONSENSUS REPORT



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

Research Priorities for Precision Medicine in NAFLD

Clin Liver Dis 27 (2023) 535–551

Paula Iruzubieta, PhD, MD[a], Ramon Bataller, PhD, MD[b], María Teresa Arias-Loste, PhD, MD[a], Marco Arrese, MD[c], José Luis Calleja, PhD, MD[d], Graciela Castro-Narro, MD, MSc[e], Kenneth Cusi, PhD, MD[f], John F. Dillon, MD[g], María Luz Martínez-Chantar, PhD[h], Miguel Mateo, MD[i], Antonio Pérez, PhD, MD[j], Mary E. Rinella, PhD, MD[k], Manuel Romero-Gómez, PhD, MD[l], Jörn M. Schattenberg, PhD, MD[m], Shira Zelber-Sagi, RD, PhD[n,o], Javier Crespo, PhD, MD[a,*], Jeffrey V. Lazarus, PhD[p,q,r,*]

KEY POINTS

- Despite its enormous burden and impact, NAFLD has received little public health attention globally, with weak and fragmented responses.
- Population-based screening is not considered cost-effective, but several studies and expert guidelines suggest that individuals with diabetes and other metabolic risk factors, such as obesity, should be considered for case-finding strategies.
- NAFLD's heterogeneity represents a major challenge in developing highly effective therapies. The identification of NAFLD phenotypes could favor precision medicine in this liver disease.
- The development of patient-centered models of care, including the use of telemedicine, is key to personalized and precision medicine in NAFLD.
- To advance the field of fatty liver disease, we developed a set of strategic research priorities addressing public health and clinical issues, including screening and diagnosis strategies, clinical trial design, multidisciplinary approaches, and novel therapies.

What is precision medicine?

Reducing error in health recommendations & medical decisions

Contemporary medicine

Precision medicine

Personalised medicine

High

Error

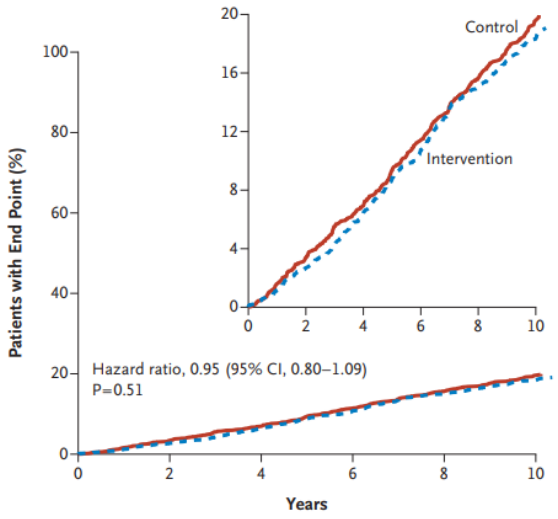
Low

novo nordisk **fonden**

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

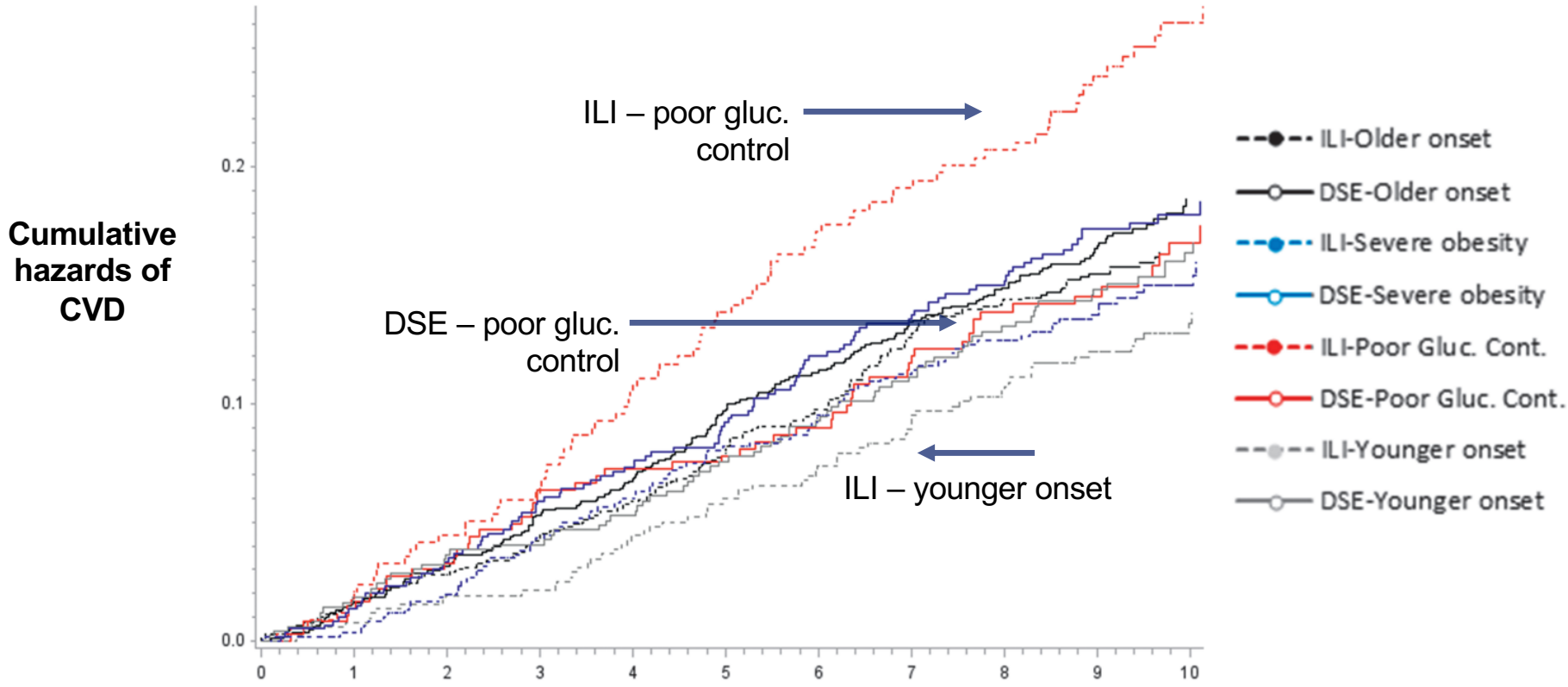
The Look AHEAD Research Group*



No. at Risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.

Reanalysis: predictors of intervention success in Look AHEAD



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

nature medicine

Article

https://doi.org/10.1038/s41591-022-02120-7

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

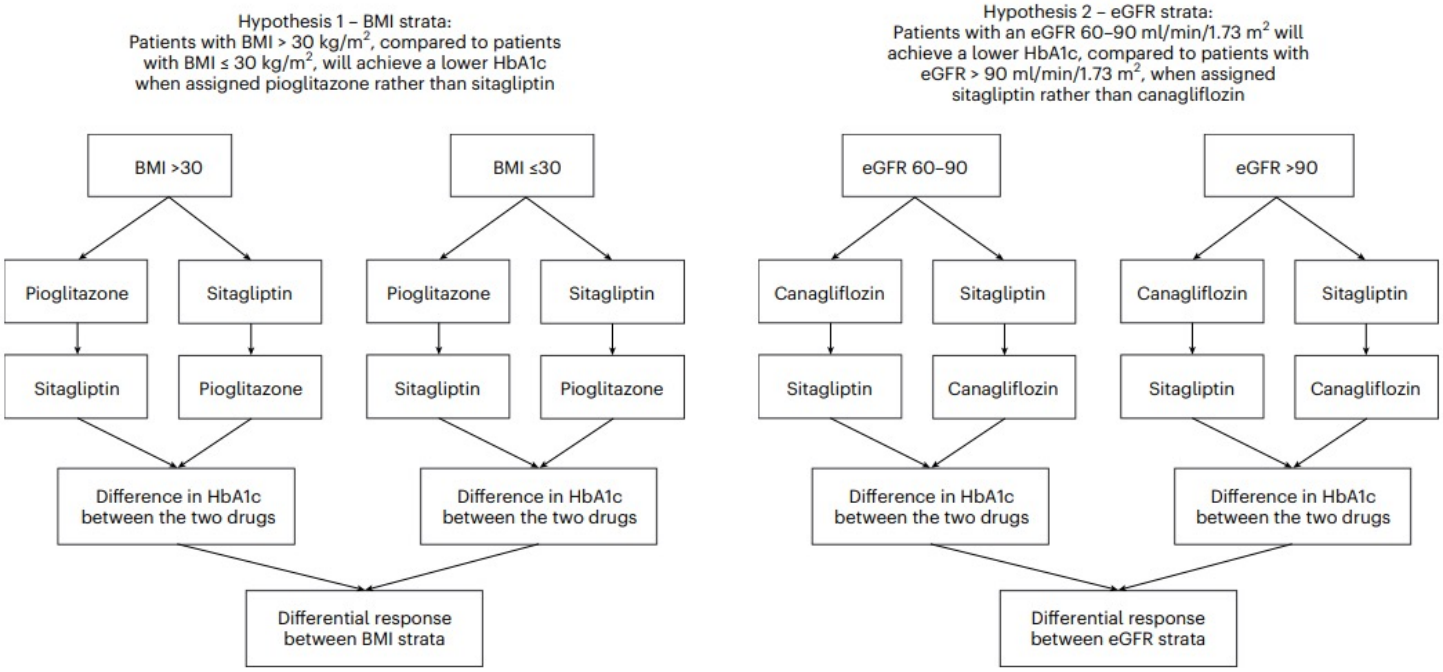
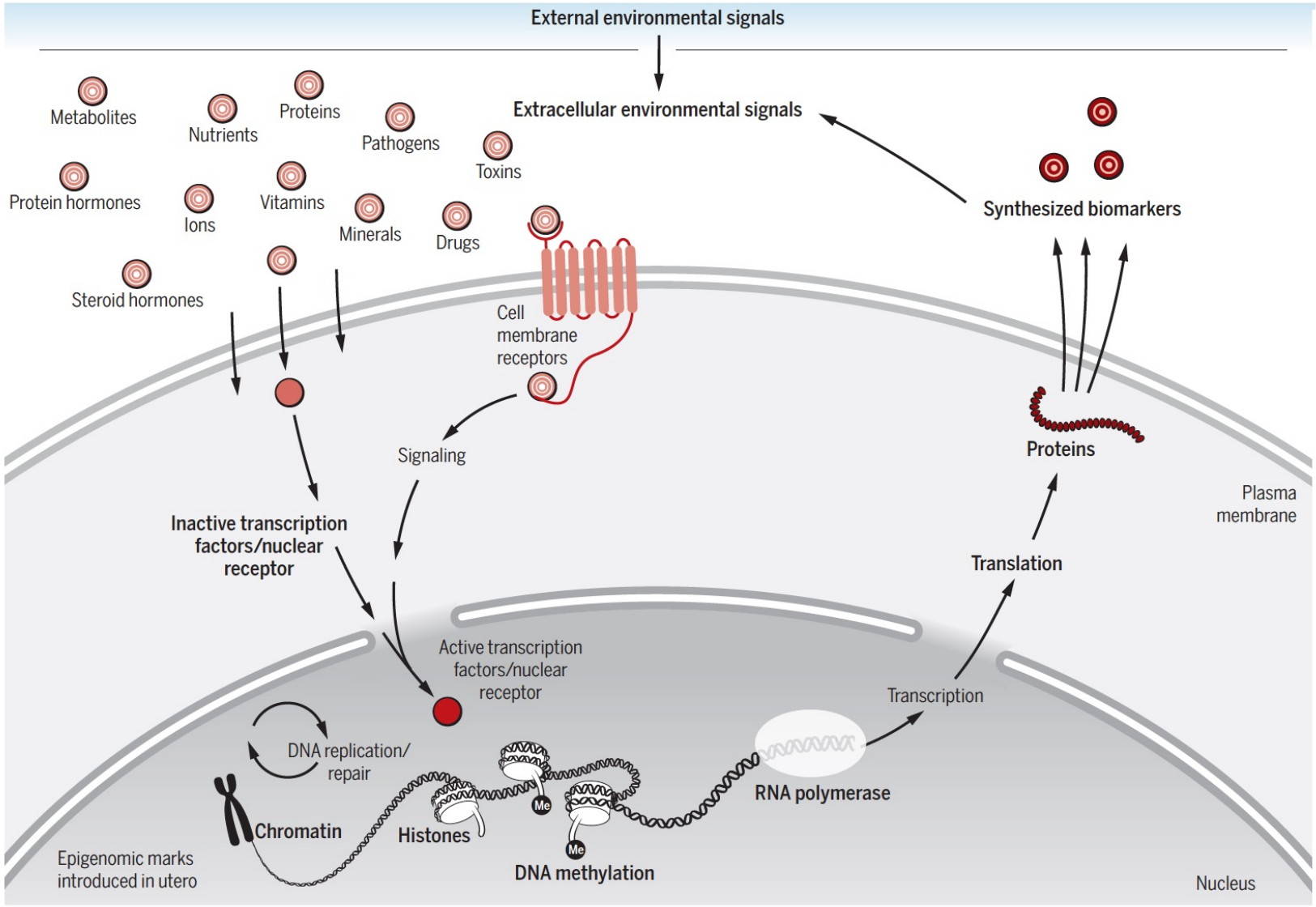
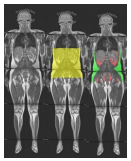


Fig. 2 | The two main hypotheses being tested in TriMaster. Flow diagram showing the comparisons and outcomes for each of the hypotheses: differential response to pioglitazone and sitagliptin between BMI strata, and differential response to sitagliptin and canagliflozin between eGFR strata.

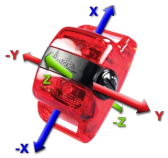


Franks PW & McCarthy MI. *Science*. 354(6308):69-73. 2016

MRI

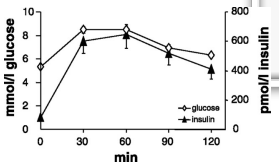


10 days ACC

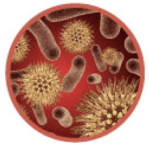


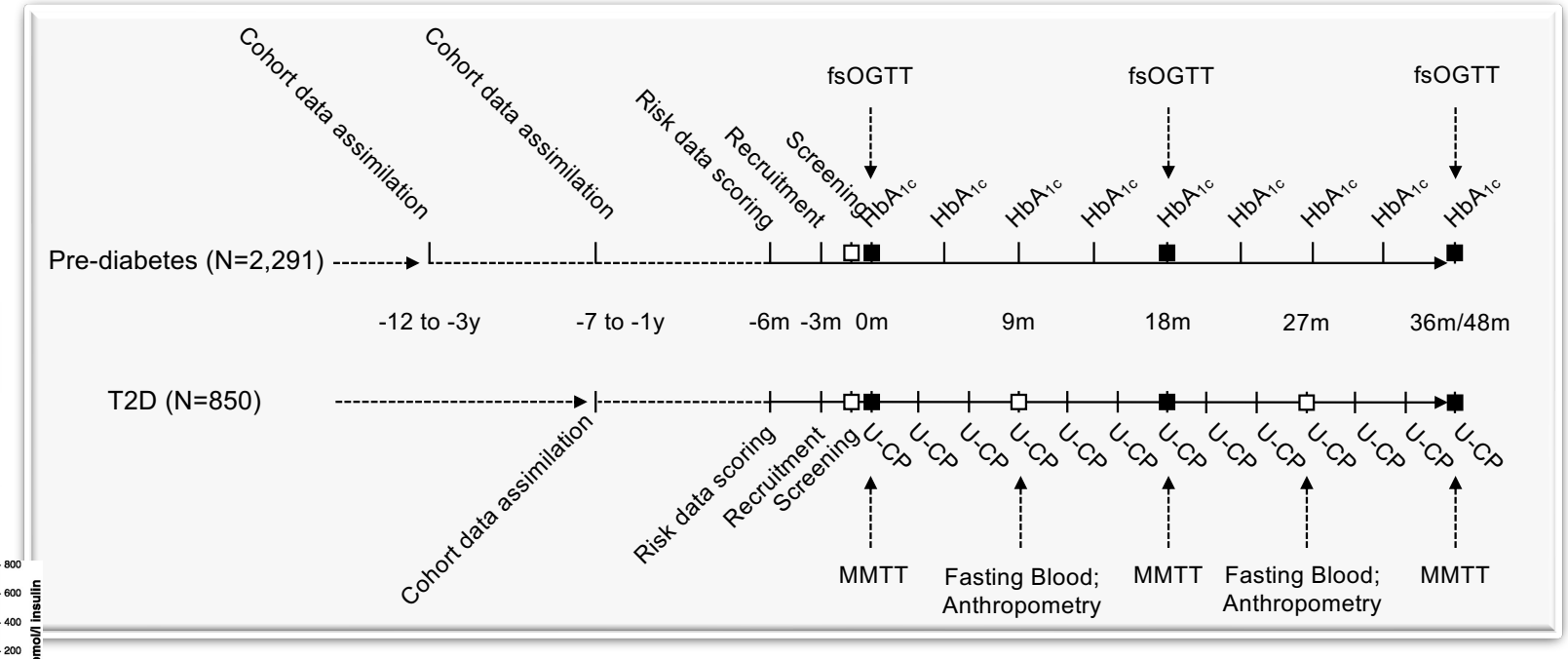
Diet records

fsOGTT



Fecal samples





Genetics

Transcriptomics

Dicer

miRNAomics

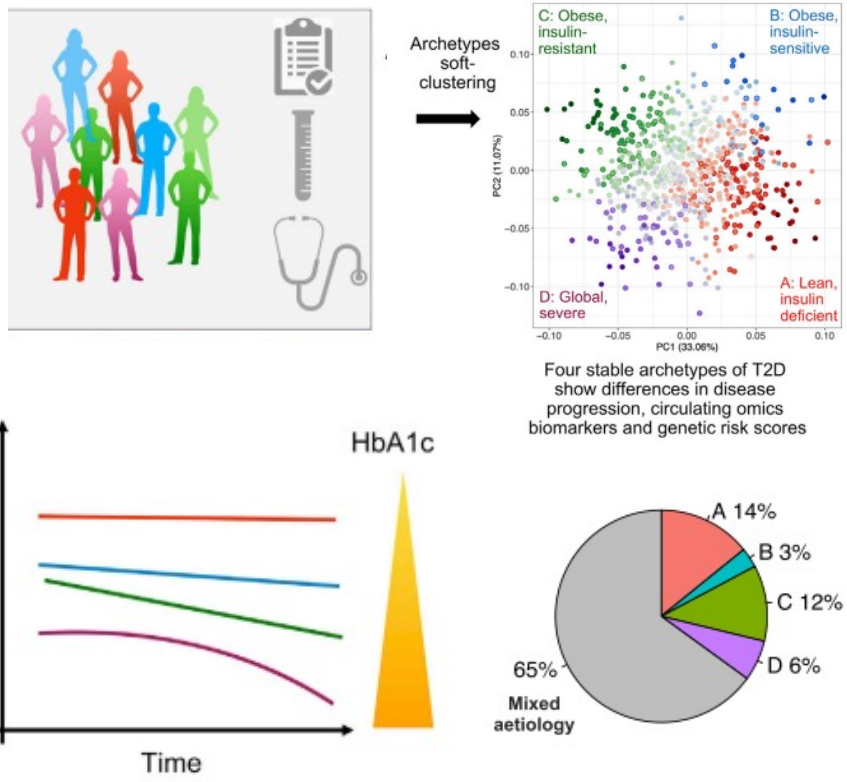
Proteomics

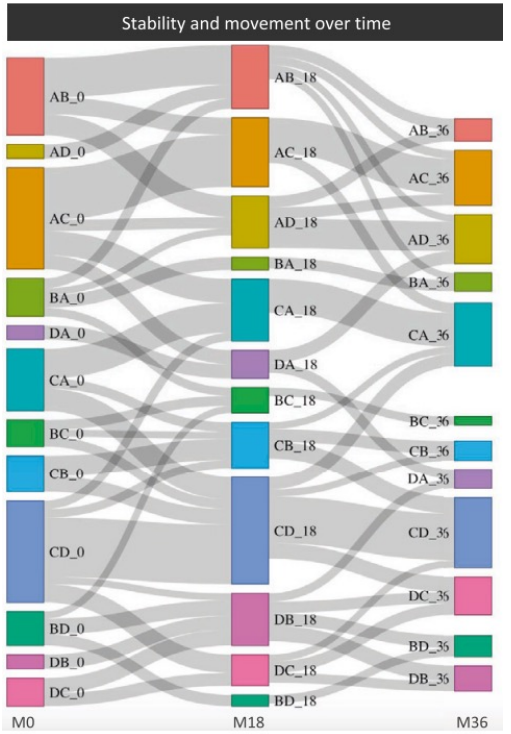
Metabolomics

Metagenomics

Koivula RW *et al*. *Diabetologia*, 62(9):1601-1615. 2019

- 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





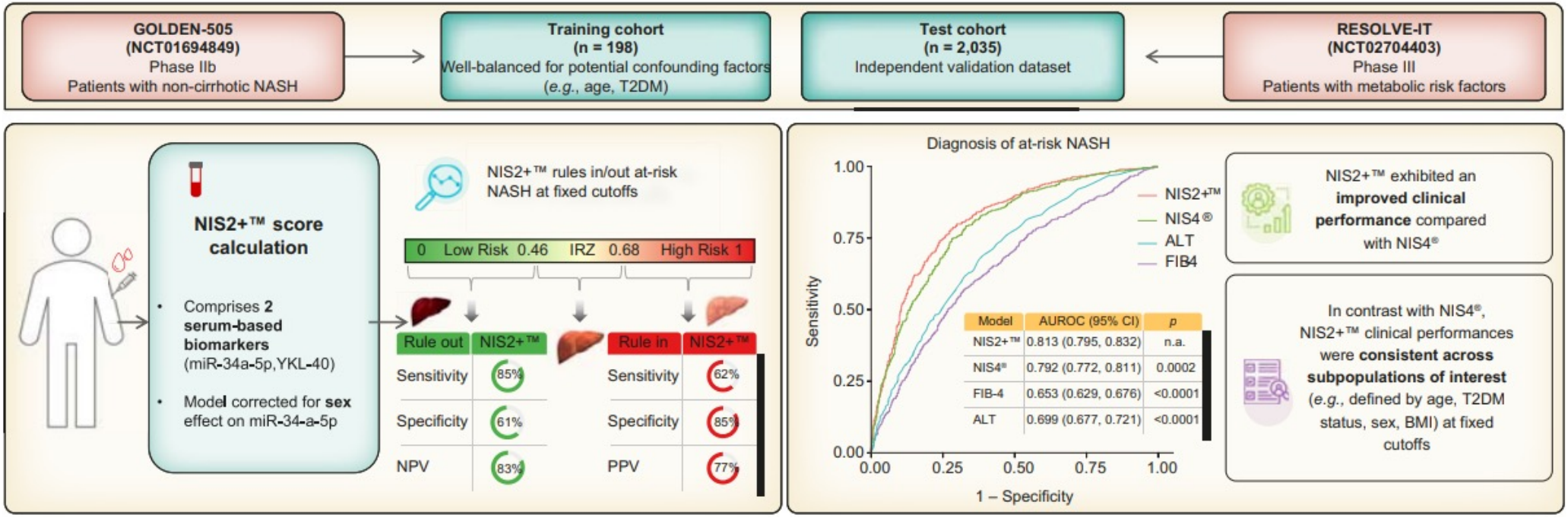
Wesolowska-Andersen A., et al. *Cell Rep Med*. 4;3(1):100477. 2022

Research Article
Innovative Diagnostics, Modelling and Digital Hepatology

JOURNAL
OF HEPATOLOGY

NIS2+™, an optimisation of the blood-based biomarker NIS4® technology for the detection of at-risk NASH: A prospective derivation and validation study

Stephen A. Harrison[1,2,†], **Vlad Ratziu**[3,†], Jeremy Magnanensi[4,*], Yacine Hajji[4], Sylvie Deledicque[4], Zouher Majd[4], Christian Rosenquist[4], Dean W. Hum[4], Bart Staels[5], Quentin M. Anstee[6,7], Arun J. Sanyal[8,‡]



nature medicine

Article

https://doi.org/10.1038/s41591-023-02539-6

Diagnostic performance of circulating biomarkers for non-alcoholic steatohepatitis

Received: 18 January 2023

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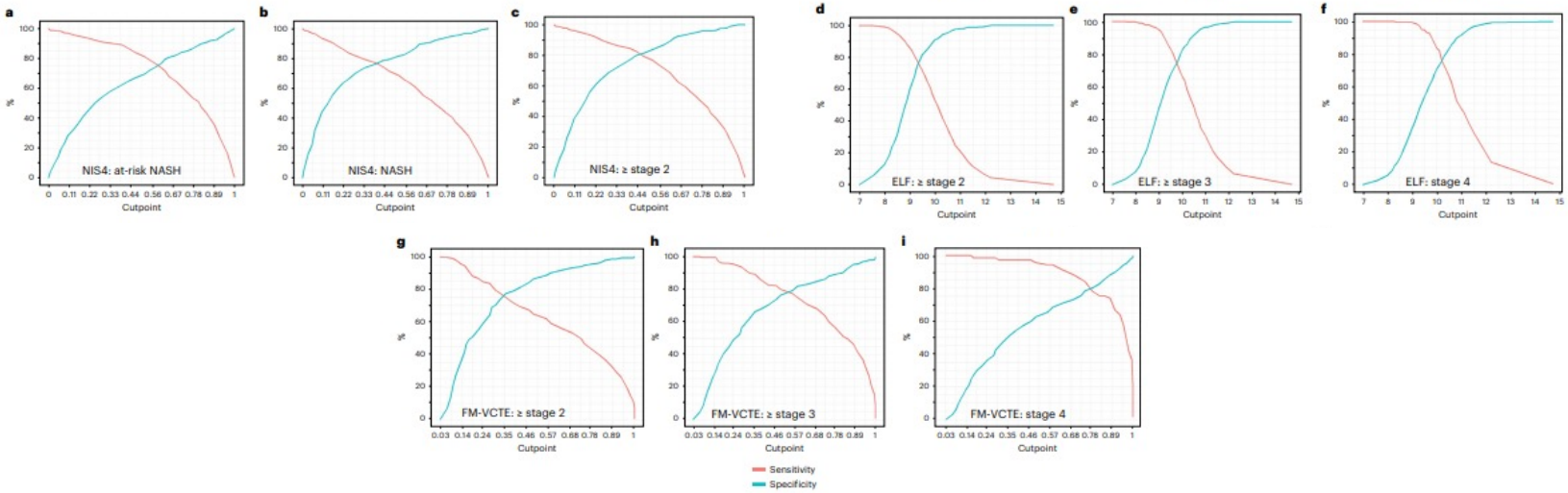
Check for updates

Arun J. Sanyal[1,16] ✉, Sudha S. Shankar[2,16], Katherine P. Yates[3], James Bolognese[4], Erika Daly[4], Clayton A. Dehn[5], Brent Neuschwander-Tetri[6], Kris Kowdley[7], Raj Vuppalanchi[8], Cynthia Behling[9], James Tonascia[3], Anthony Samir[10], Claude Sirlin[11], Sarah P. Sherlock[12], Kathryn Fowler[11], Helen Heymann[13], Tania N. Kamphaus[13], Rohit Loomba[14,17] & Roberto A. Calle[15,17]

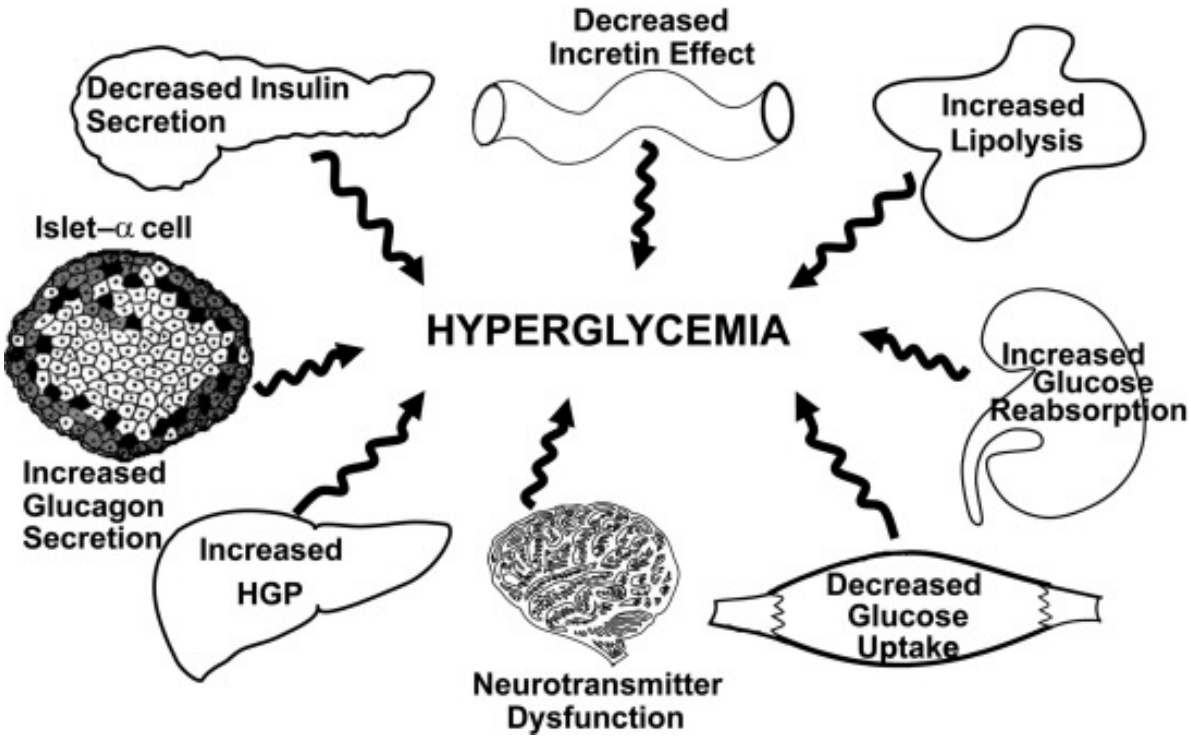


DIABETES, VOL. 58, APRIL 2009

BANTING LECTURE

From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

Ralph A. DeFronzo

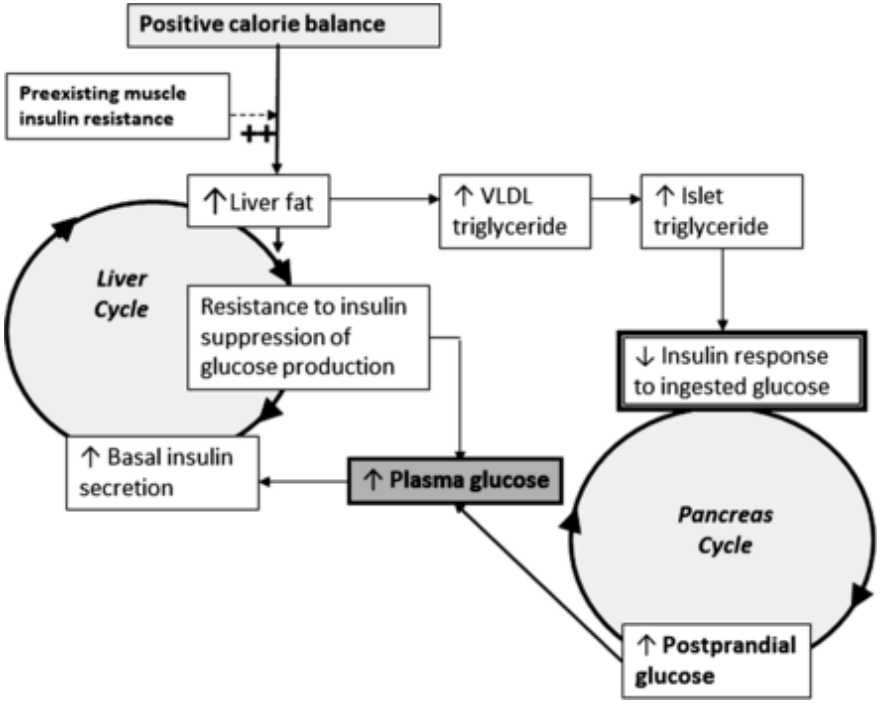


DIABETES CARE, VOLUME 36, APRIL 2013

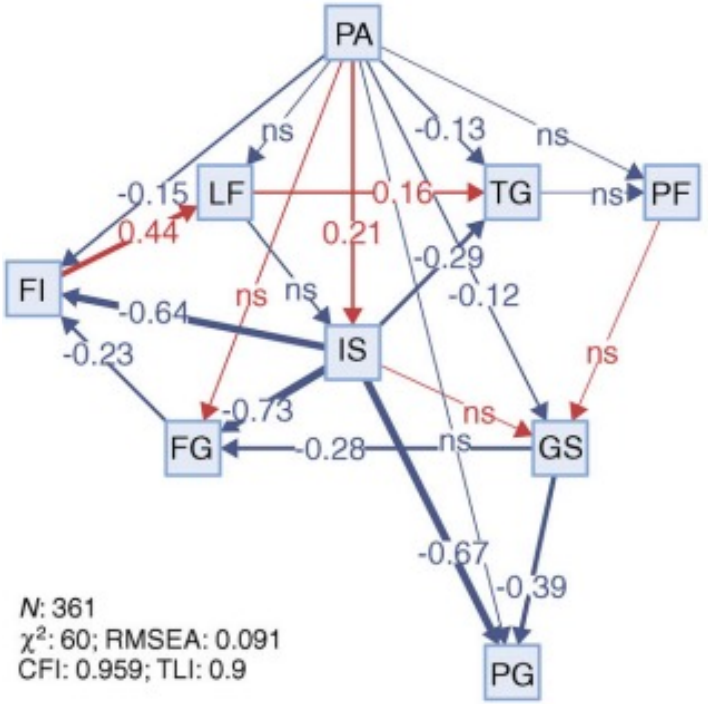
Type 2 Diabetes

Etiology and reversibility

ROY TAYLOR, MD, FRCP



Testing the Twin Cycle hypothesis using structural equation modeling

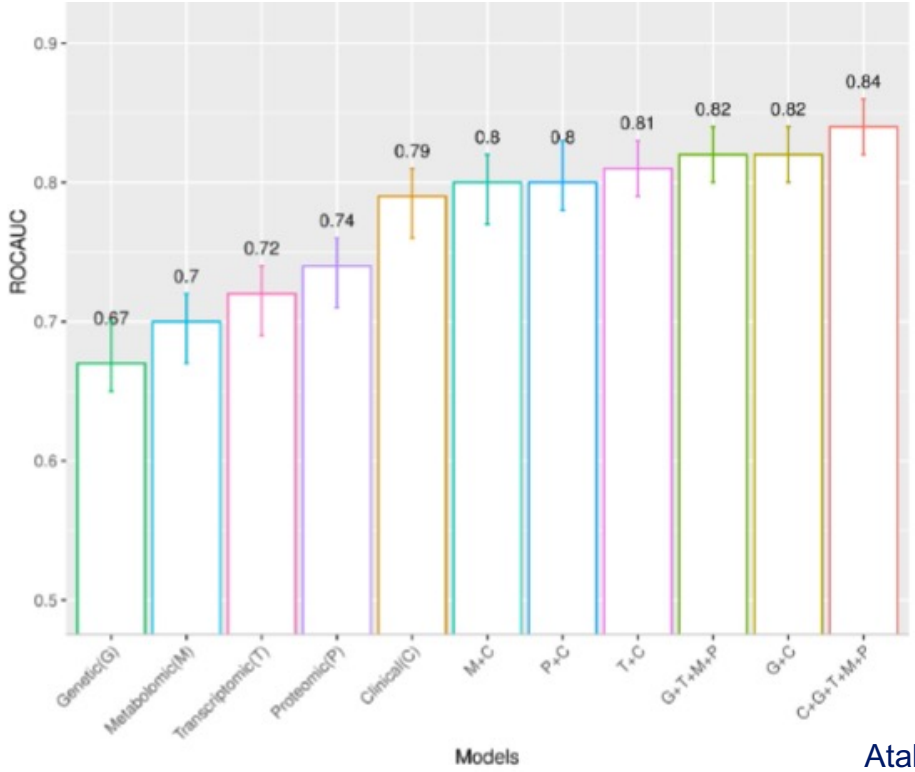


Koivula R.W., *et al*. *Diabetologia*, 63(4):744-756. 2020

RESEARCH ARTICLE

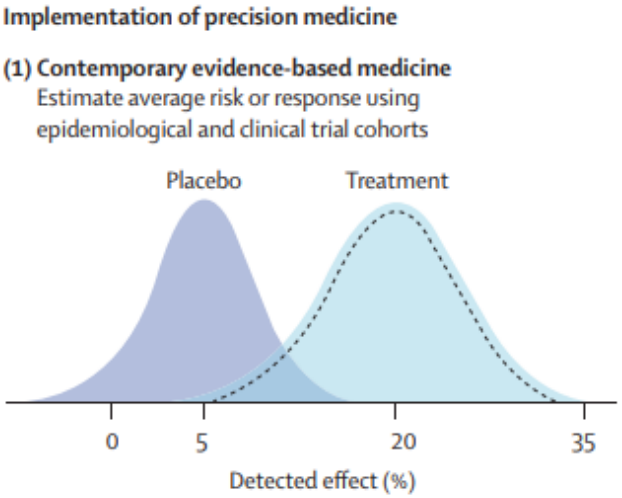
Predicting and elucidating the etiology of fatty liver disease: A machine learning modeling and validation study in the IMI DIRECT cohorts

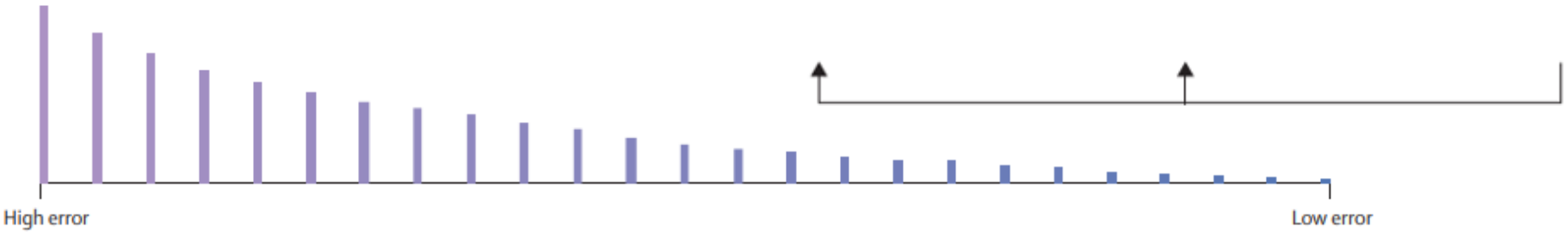
NaEme Atabaki-Pasdar



Atabaki-Pasdar N, et al. *PLOS Med*. 2020

Precision medicine for cardiometabolic disease: a framework for clinical translation





Franks P.W., et al. *Lancet Diab & Endo*. (in press)

6 key take-home messages

Great progress in diagnostic sub-classification in type 2 diabetes (same methods could be applied to MAFLD)

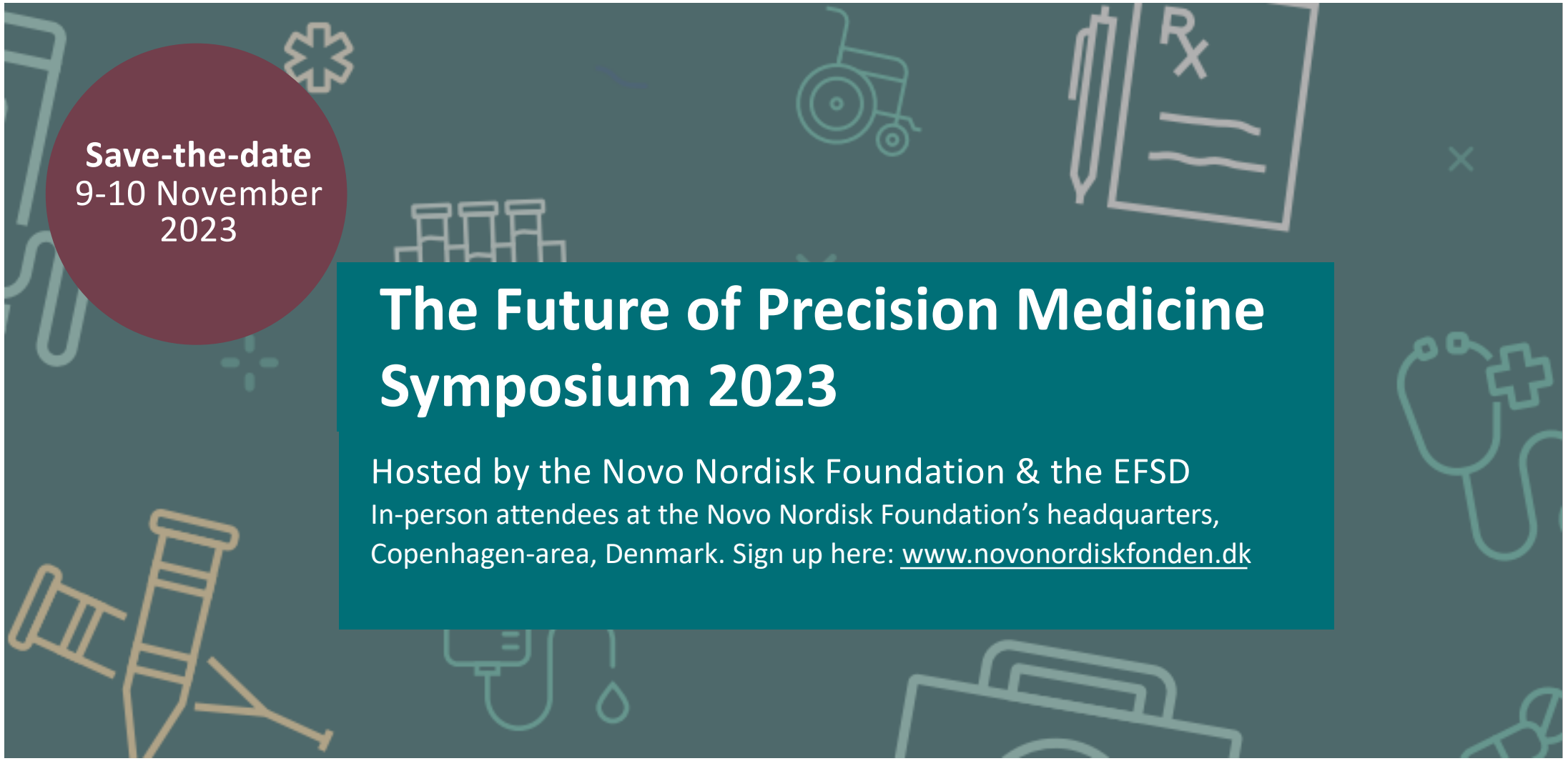
Published data are not standardised, making data synthesis v. challenging

Need for common standards for study design

Need for prospective precision medicine trials

Need for data from non-European ancestry populations

Genomics is not the panacea for complex disease precision medicine



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