

9⁰ CONGRESSO CONGIUNTO **SID-AMD** **Sicilia**

»» Il diabete oggi tra prevenzione,
nuovi farmaci e tecnologia:
un ponte verso il futuro

Palermo, 15/16 novembre 2024 Hotel La Torre



UNIVERSITÀ
DEGLI STUDI
DI PALERMO

promise
Department of Prevention and Social, Maternal-Infantile, Internal Medicine and Specialties of Endocrinology "G. L'Abbate"



Carla Giordano, M.D.

^ Il Futuro Perfetto ^
della Diabetologia

Conflicts of interest:

dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche:

Novo Nordisk, Eli Lilly, Boehringer, IBSA, Abbott, Sanofi, Savio, Penta, Dompè

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Precision medicine in diabetes: a Consensus Report from the ADA and EASD

Precision diabetes medicine refers to an approach to optimise the diagnosis, prediction, prevention or treatment of diabetes by integrating multidimensional data, accounting for individual differences. The major distinction from standard medical approaches is the use of complex data to characterise the individual's health status, predisposition, prognosis and likely treatment response

From Chung et al, 2020 [6]

Regulatory considerations for advancing precision medicine in T1DM

Stage of Disease	Scientific Gap	Implications
Primary Prevention	Identifying very high-risk individuals beyond current genetics Identifying effective preventive interventions with sufficient safety to study broadly	With low disease prevalence, feasible prevention trials would benefit from precision medicine–guided enrichment (and would also inform targeted preventive use clinically) Broad vaccination programs require interventions that are highly protective and very safe/well tolerated
Secondary Prevention	Practical means to identify individuals with subclinical disease Full understanding of the immune mediators and propagators of β-cell damage	Immune-based interventions carry safety/toxicity risks requiring targeting of use both in clinical trials and subsequent clinical deployment Better understanding of the inciting and sustaining immune mechanisms would allow for better targeting of intervention vs. broad immunosuppressive approaches
Treatment	No apparent “precision” considerations in choice of insulin therapy/approach	Insulin therapy likely to remain more “personalized” than “precise,” absent new science

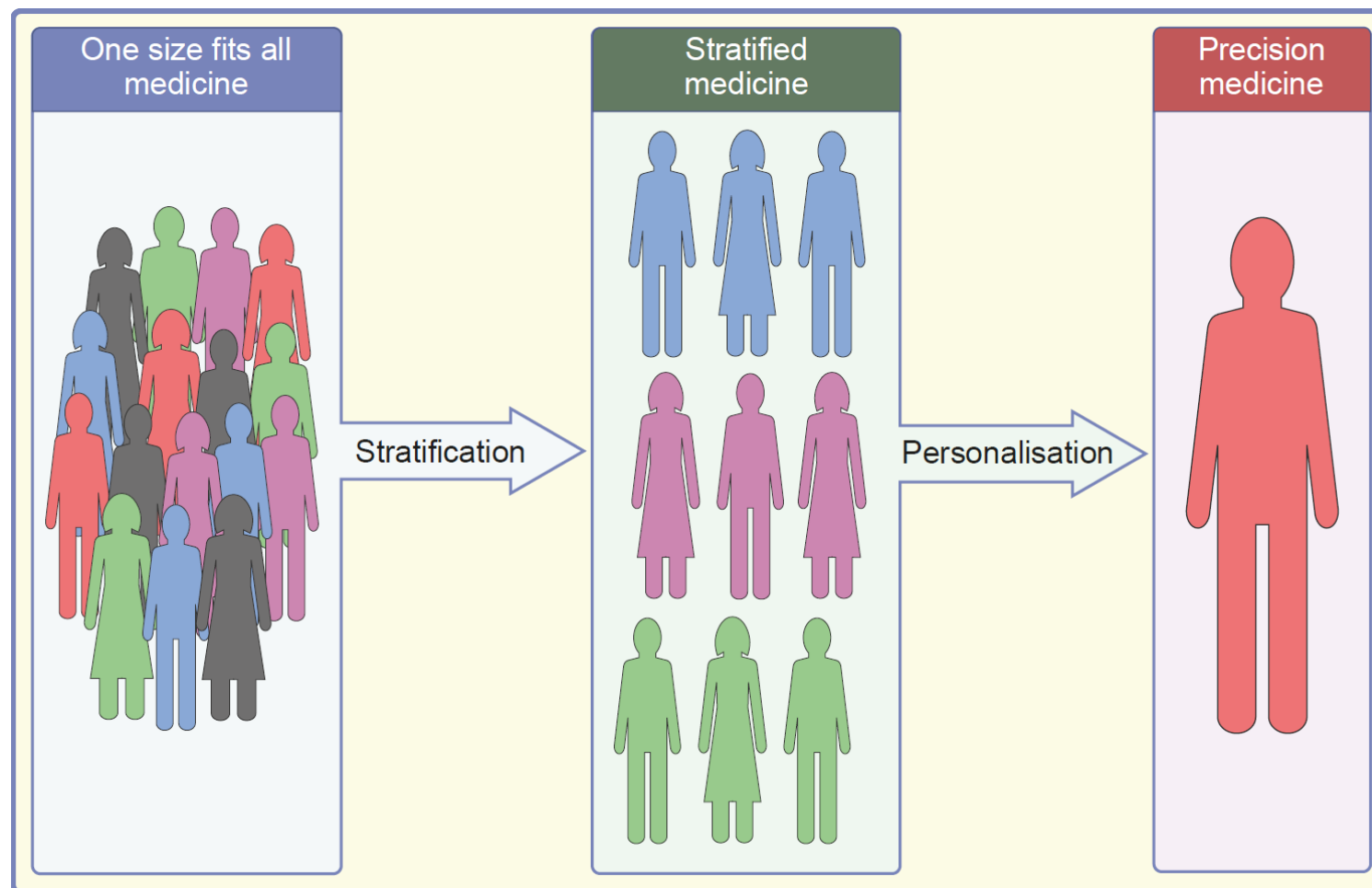
Diabetes Care 2016;39:1874–1878 | DOI: 10.2337/dc16-1762

Regulatory considerations for advancing precision medicine in T2DM

Stage of Disease	Scientific Gap	Implications
Prevention	Identification of specific mechanisms leading to disease (beyond clinical risks of obesity, diet, sedentary lifestyle)	Prevention likely to remain diet and exercise in at-risk individuals particularly showing early signs of dysglycemia ± nontargeted use of hypoglycemic agents
Treatment	Lack of data to inform matching of specific underlying disease characteristics in a given patient to optimal therapeutic approach Predictive biomarkers for secondary complications (micro/macrovacular)	Therapy will remain guided by expert guidelines and empiric treatment Would allow for tailoring of therapies not just to achieve a glycemic goal but to more precisely mitigate risks of long-term complications

Diabetes Care 2016;39:1874–1878 | DOI: 10.2337/dc16-1762

Stratified and precision medicine



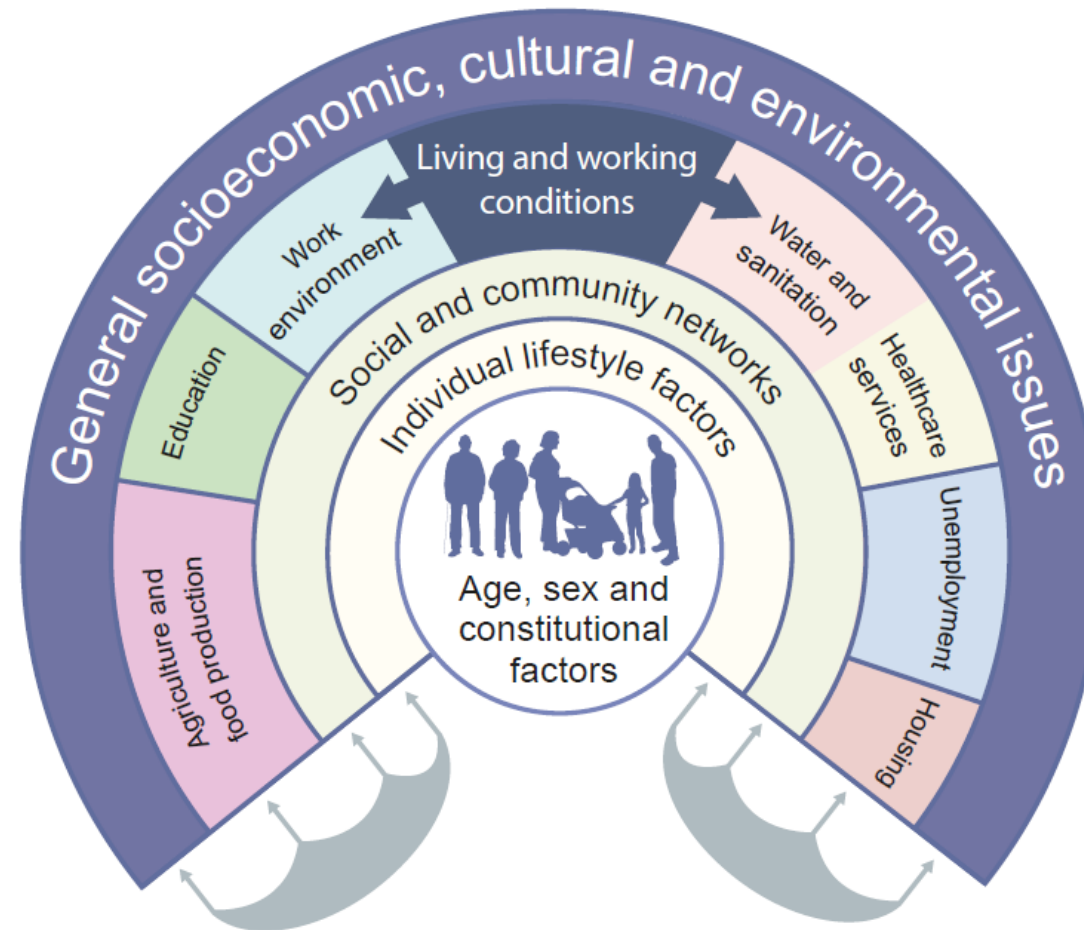
Griffin (2022) Diabetologia DOI 10.1007/s00125-022-05782-7

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Diabetologia

The main determinants of health. Adapted from Dahlgren G, Whitehead M, 2007



Griffin (2022) Diabetologia DOI 10.1007/s00125-022-05782-7

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Diabetologia

INTELLIGENZA ARTIFICIALE

L'intelligenza artificiale si riferisce alla **capacità di una macchina di svolgere compiti intelligenti**, come il riconoscimento di immagini e modelli, la pianificazione di azioni, la risoluzione di problemi, la comprensione del linguaggio e il riconoscimento di oggetti e suoni.

Più in generale, è **l'applicazione di metodi statistici a grandi quantità di dati per apprendere modelli e fare previsioni quando vengono presentati nuovi dati.**

Perchè è importante l'intelligenza artificiale in campo medico?

- La **disponibilità di dati in ambito medico** è cresciuta enormemente così come le fonti da cui essi provengono.
- Accanto ai **dati tradizionali “strutturati”**, rappresentabili in righe e colonne come avviene con i fogli di Excel o con i principali database (cartelle cliniche, Medline, linee guida e database biomolecolari e genetici) sono sempre più disponibili **dati non strutturati** (come testi, immagini, suoni, sensori, dispositivi indossabili come magliette, braccialetti, orologi intelligenti, conversazioni provenienti dai social media).
- **Gli algoritmi di intelligenza artificiale in ambito medico sono usati per interpretare questa enorme mole di dati e per identificare possibili relazioni di causa-effetto tra i dati stessi e le patologie di cui un paziente soffre.**

1943
Il modello
McGillach & Pitts
descrive per la
prima volta il
neurone come unit
logica artificiale.

1940s
Le tre leggi
della robotica
di Isaac Asimov,
alle quali
obbediscono
tutti i robot
postmoderni.

1946
: il primo
re moderno
elaborare
comaricci.
titante da
e valvole.

1

1958 The Computer and the Brain: il matematico John von Neumann imita le funzioni neurali con l'uso di ripetitori telegrafici e valvole

1956
Il matematico John McCarthy introduce per la prima volta il termine "intelligenza artificiale", in occasione di una conferenza al Dartmouth college di Hannover.

1950
Il test di Turing
per vedere se un
computer può essere
considerato
intelligente.

Narvin Minsky e Dean Edmonds creano la prima rete neurale: Sears.

1959
Nasce Adaline e
Madeline, la prima
rete neurale applicata
a un problema concreto:
eliminare gli echi
sulle linee
telefoniche.

1966/72
Viene progettato
Shakey, il primo
robot mobile
"intelligente"
su due ruote
(nel 1970 la
rivista Life
e il National
Geographic
gli dedicano
la copertina).

1968
2901: Odiasse
nelle sporte:
il file di
Stanley Kubrick.

1969
Il Carnegie Institute of Technology programma Bedral, l'algoritmo che costruisce la struttura di una molecola a partire dai dati dello spettrometro di massa.

1957
Frank Rosenblatt
Sesla Perceptron
una macchina di
tonnellate che
livello software
e hardware sia
una rete di
otto neuroni.

1980

1987
A San Diego si tiene
la prima conferenza
sui sistemi neurali
1800 persone
19 società
nasce la Società
internazionale
sui sistemi
neurali



2001
A Wall Street
gli algoritmi
hanno battuto
gli operatori
finanziari umani.

1999
dotato di
lie Sony,
giornale
nel 2017.

2005

2009

La Commissione europea lancia lo Human Brain Project per realizzare entro il 2023 una simulazione completa del cervello umano.

IBM annuncia la prima applicazione commerciale di Watson in oncologia Memorial Sloan-Kettering cancer center.

2011

Apple integra
l'assistente
vocale Siri
nell'iPhone 4s.

Il supercomputer Watson vince un milione di dollari nel quiz show Jeopardy

2016
Google
il progetto
DeepMind Health
di Google
per migliorare
le cure
analitiche.

2007

Con la pubblicazione dell'articolo "Learning multiple layers of representation" di Geoff Hinton nasce il **deep learning**.

1996
In una partita a scacchi
il computer Deep Blue
dell'Ibm batte il campione
russo Garry Kasparov.

1998

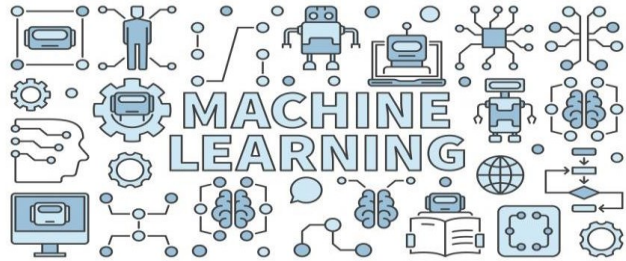
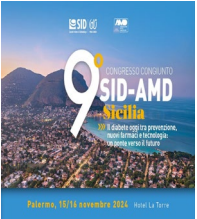
2014
Nasce il chip
Truth North
ispirato
all'architettura
del cervello umano:
esegue compiti
sottificati
in tempo reale.
Nasce appunto
dall'Ibm e dalla
Cornell university.

2017
Ibm investe
240 milioni
di dollari in
un laboratorio
dedicato
all'intelligenza
artificiale.

Xianbo,
il chatbot cinese
della microsoft,
scrive poesia.

Microsoft e Softjam presentano il sistema Sj-Ckd per l'identificazione di pazienti cronici sintomatici.

Un algoritmo sviluppato alla Stanford University viene implementato con successo per la diagnosi dei tumori della pelle.

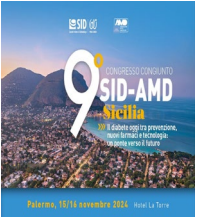


Machine Learning

è una disciplina volta ad aumentare la conoscenza umana attraverso l'uso della tecnologia.

è un sottoinsieme dell'intelligenza artificiale
in cui il software
analizza i dati, ne riconosce le caratteristiche e
"impara" dal loro esame

In sostanza, gli algoritmi di Machine Learning apprendono informazioni e ridefiniscono il loro comportamento direttamente dai dati, senza modelli matematici ed equazioni predeterminate.



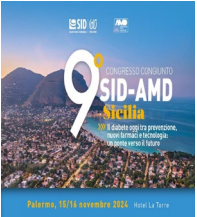
Il **Machine learning** genera maggiore valore dai dati perché effettua:

- ✓ **analisi di tipo descrittivo** (reportistica del passato)
- ✓ **analisi predittive**: attraverso l'identificazione automatica di specifici pattern all'interno dei dati, evidenzia delle correlazioni che consentono di esprimere delle “**predizioni**” con ragionamenti di tipo induttivo tipici della mente umana.
- ✓ **analisi prescrittive**: i software di IA trasparente (non black box) che esplicitano le regole alla base dei modelli predittivi possono fare delle simulazioni per capire come si possono modificare gli outcome





INTELLIGENZA ARTIFICIALE, DIGITAL HEALTH E DIABETOLOGIA



La **Diabetologia** si trova ad affrontare diverse sfide:

- il numero sempre minore di diabetologi
- il numero crescente dei pazienti
- la riduzione del tempo di visita
- la sempre maggiore complessità della patologia sia dal punto di vista clinico sia assistenziale
- la difficoltà di raggiungimento degli obiettivi
- il carico crescente di gestione della patologia sia per l'operatore sanitario sia per il paziente
- nuovi modelli assistenziali
- l'accessibilità alle cure
- la sostenibilità

Le nuove tecnologie digitali e l'utilizzo dell'intelligenza artificiale rappresentano sicuramente una grande opportunità.



ADA/EASD Precision Medicine in Diabetes Initiative: An International Perspective and Future Vision for Precision Medicine in Diabetes

Diabetes Care 2022;45:261–266 | <https://doi.org/10.2337/dc21-2216>

Key milestones and timelines of the ADA/EASD PMDI



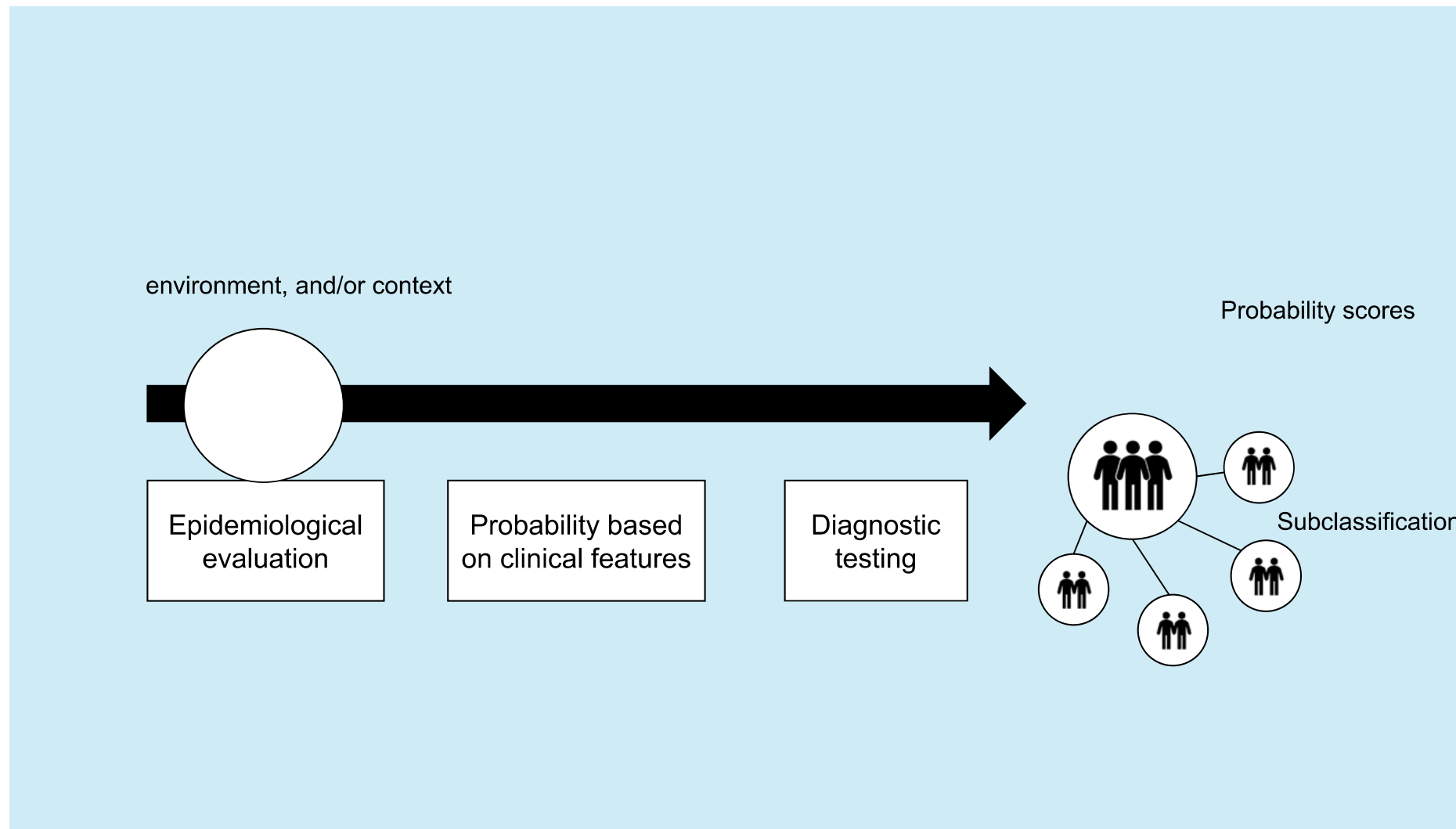
The Consensus Report named five key pillars, or domains, of precision diabetes medicine:

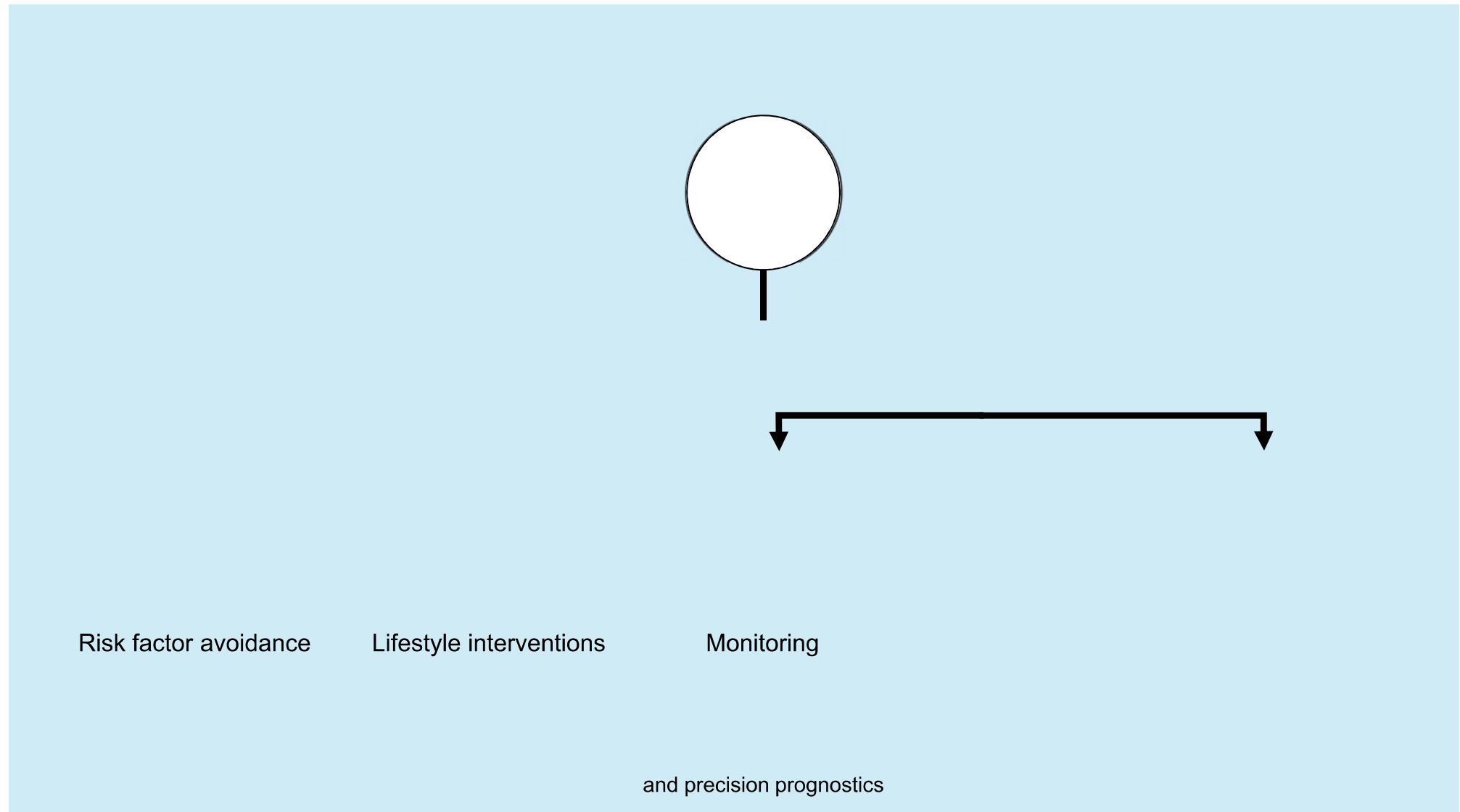
- **precision diagnostics**
- **precision prevention**
- **precision treatment**
- **precision prognostics**
- **precision monitoring**



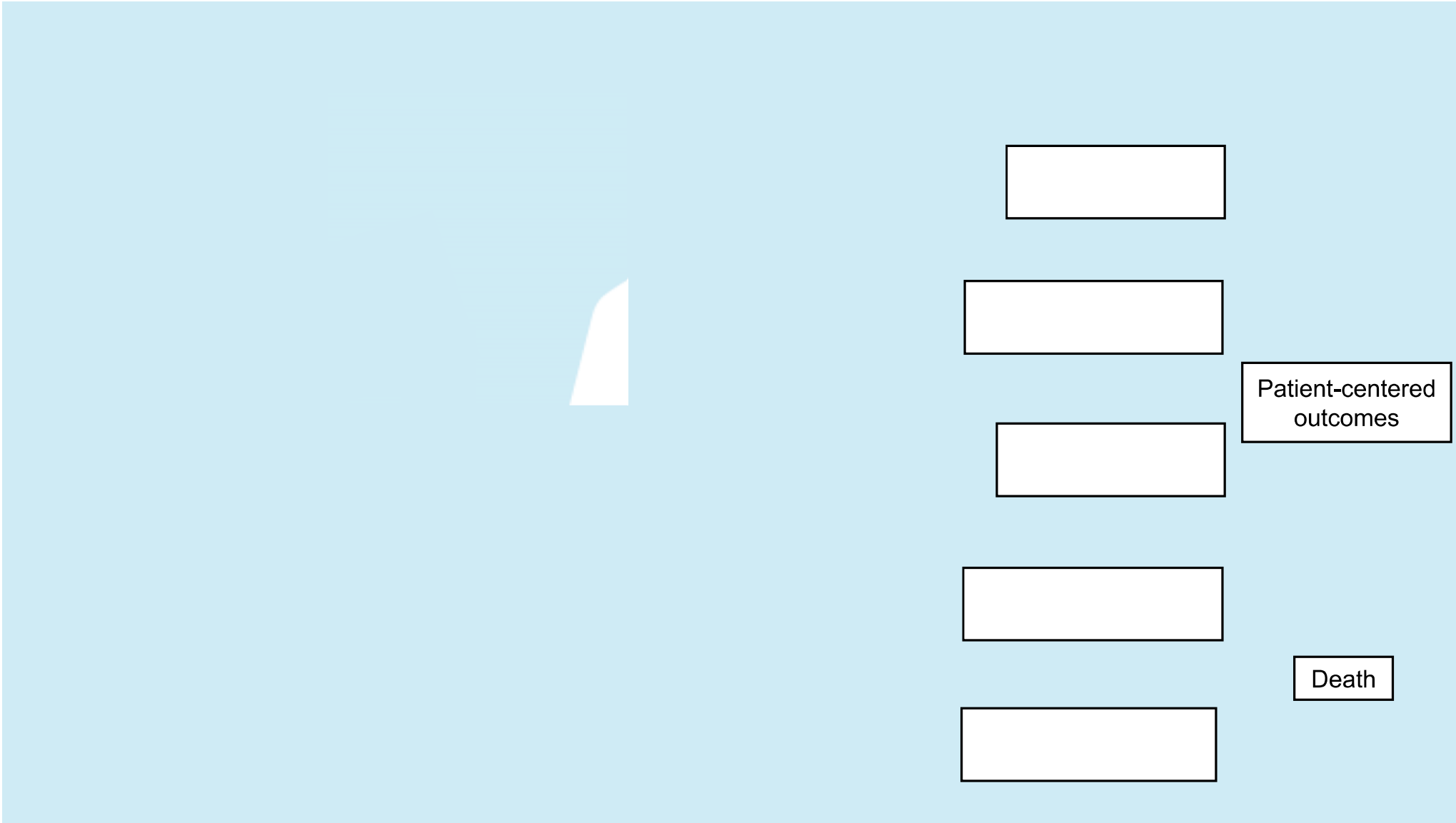
Text Box 1—Definitions

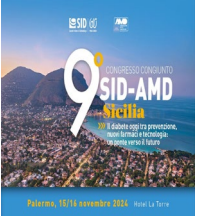
- **Precision diagnosis** involves refining the characterization of the diabetes diagnosis for therapeutic optimization or to improve prognostic clarity using information about a person’s unique biology, environment, and/or context.
 - Precision diagnostics may involve subclassifying the diagnosis into subtypes, such as is the case in MODY, or utilizing probabilistic algorithms that help refine a diagnosis without categorization.
 - Careful diagnosis is often necessary for successful precision therapy, whether for prevention or treatment. This is true where subgroup(s) of the population must be defined, within which targeted interventions will be applied, and also where one seeks to determine whether progression toward disease has been abated.
 - Precision diagnosis can be conceptualized as a pathway that moves through stages, rather than as a single step. The diagnostic stages include 1) an evaluation of prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex, and ancestry; 2) probability based on clinical features; and 3) diagnostic tests that are interpreted in the light of 1) and 2). A diagnosis in precision medicine is a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state.
- **Precision therapeutics** involves tailoring medical approaches using information about a person’s unique biology, environment, and/or context for the purposes of preventing or treating disease (see *Precision prevention* and *Precision treatment*, below).
- **Precision prevention** includes using information about a person’s unique biology, environment, and/or context to determine their likely responses to health interventions and risk factors and/or to monitor progression toward disease.
 - Precision prevention should optimize the prescription of health enhancing interventions and/or minimize exposure to specific risk factors for that individual. Precision prevention may also involve monitoring of health markers or behaviors in people at high risk of disease, to facilitate targeted prophylactic interventions.
- **Precision treatment** involves using information about a person’s unique biology, environment, and/or context to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome, while reducing unnecessary side effects.
 - Today, the objective of precision therapy is to maximize the probability that the best treatment of all those available is selected for a given patient. It is possible that in the future, precision diabetes medicines will be designed according to the biological features of specific patient subgroups, rather than for the patient population as a whole.
- **Precision prognostics** focuses on improving the precision and accuracy with which a patient’s disease-related outcomes are predicted using information about their unique biology, environment, and/or context.
 - The focus of precision prognostics includes predicting the risk and severity of diabetes complications, patient-centered outcomes, and/or early mortality.
- **Precision monitoring** may include the detailed assessment of biological markers (e.g., continuous glucose monitoring), behaviors (e.g., physical activity), diet, sleep, and psychophysiological stress.
 - Precision monitoring can be achieved using digital apps, cutaneous or subcutaneous sensors, ingestible sensors, blood assays etc.
 - The intelligent processing, integration, and interpretation of the data obtained through precision monitoring are key determinants of success.
 - Precision monitoring may be valuable for precision prevention (e.g., in T1D), precision diagnostics (e.g., where diagnoses are based on time-varying characteristics), and precision prognostics (e.g., where disease trajectories are informative of the development of key outcomes).





Consensus Report
Diabetes Care Volume 43, July 2020



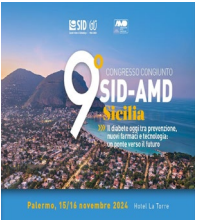


The path to precision diabetes medicine. HEA, health economic assessment. Adapted from Fitipaldi et al.



Consensus Report
Diabetes Care Volume 43, July 2020

Key steps in the iterative process of implementing the PDML into clinical practice



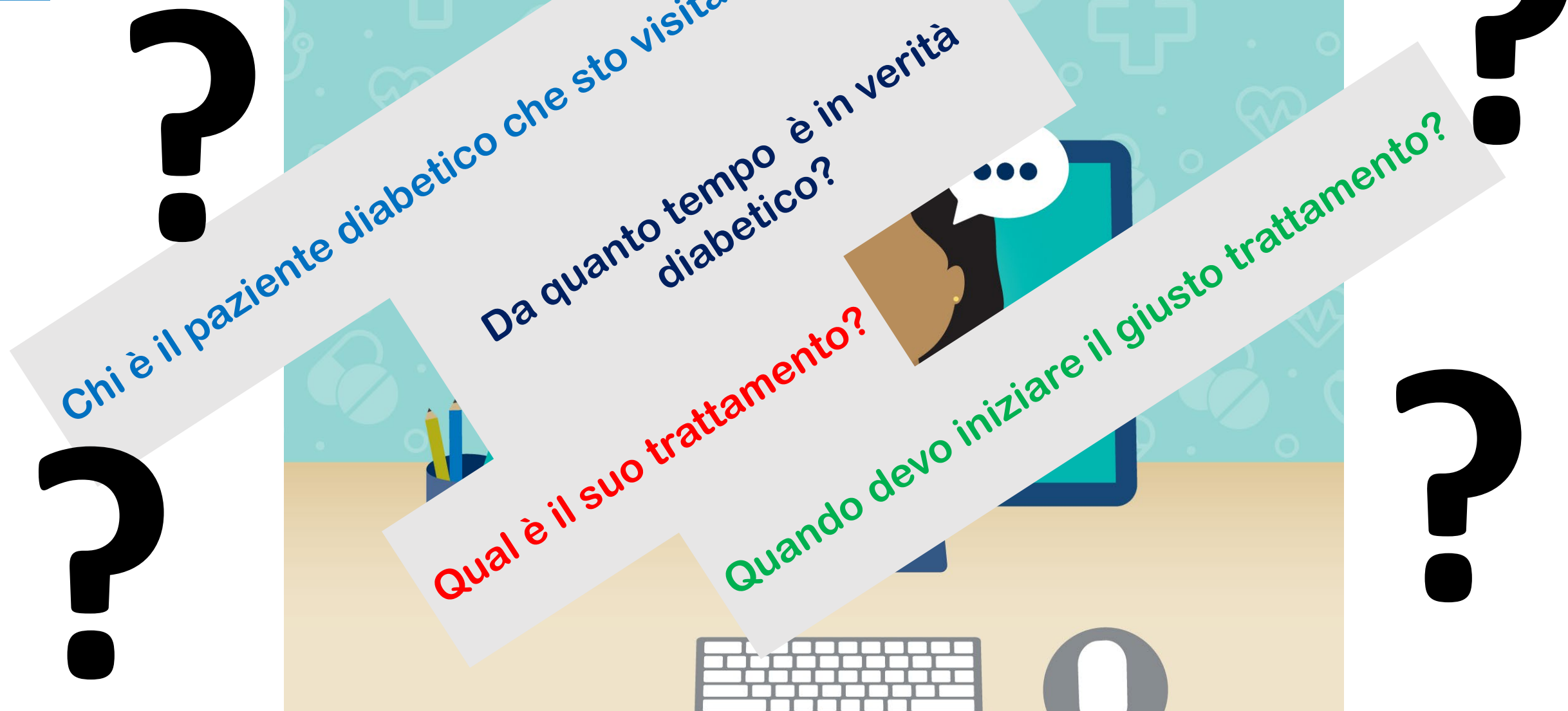
Expected tasks performed at clinical consultations in the USA

Clinical priority	Measurement	Frequency
History, physical and emotional	Blood pressure	Every visit
	Weight	Every visit
	Foot examination (monofilament)	Every visit (annually)
	Dilated eye examination	Annually
	Dental	Bi-annually
	Depression	Annually
	Medication review	Every visit
General care	Tobacco status	Every visit
	Periodic history and physical examination/ Pap or prostate	As indicated
	Mammogram/chest X-ray	Every 1-2 years
	Colorectal cancer	After age 50
Laboratory	Electrocardiogram	As indicated
	HbA _{1c}	Quarterly
	Urine albumin: creatinine ratio; serum creatinine	Annually
	LDL cholesterol; triglycerides; HDL cholesterol; non-HDL cholesterol; total cholesterol	Annually
Vaccine	Flu	Annually
	Pneumovax	Revaccinate at age >65 if initial >5 years ago and age <65
	Purified protein derivative tuberculosis skin test, tetanus-diphtheria-pertussis vaccine	As indicated
Self management: blood glucose monitoring, physical activity, nutrition		

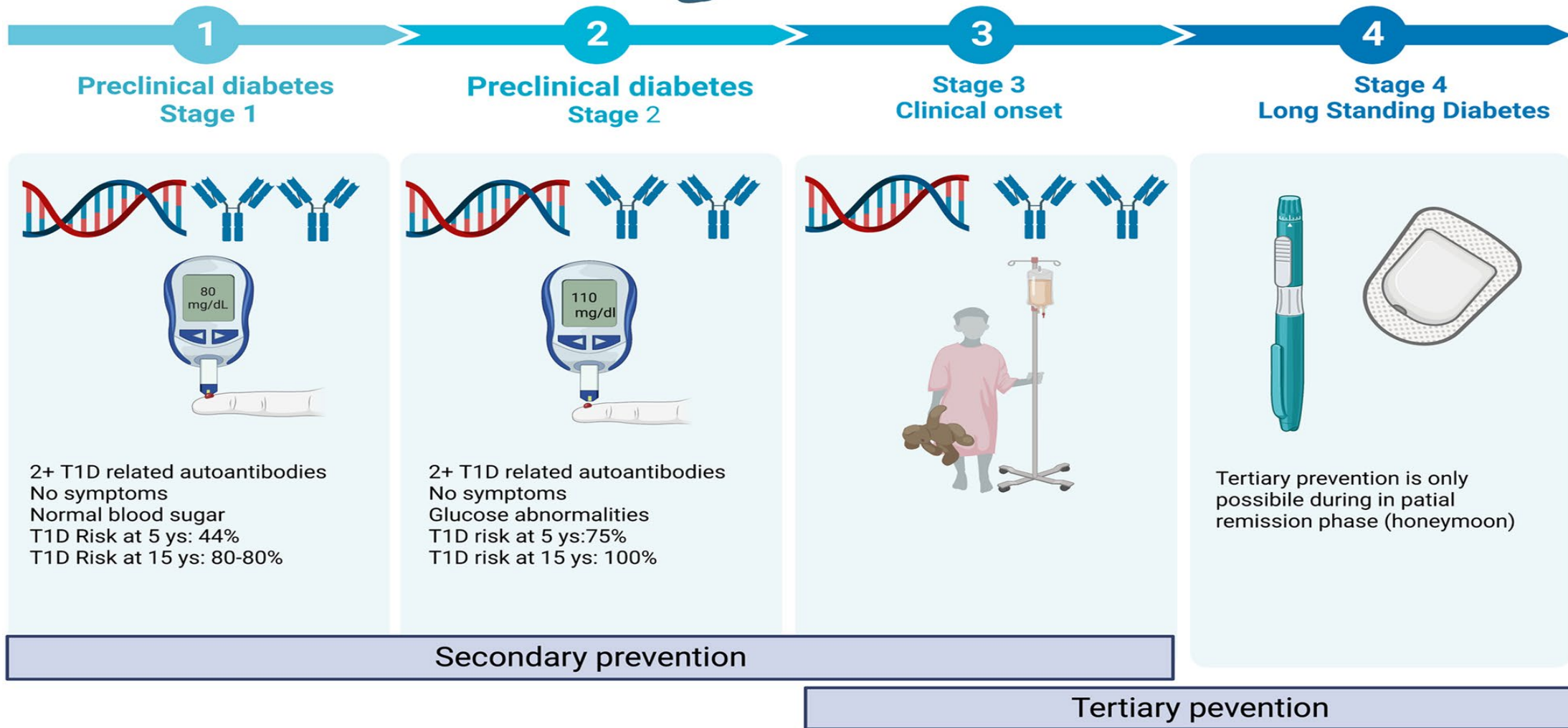
Expected tasks performed at clinical consultations in the UK

Clinical priority	Healthcare essential	Frequency
History, physical and emotional	Have your blood pressure measured	At least annually
	Have your eyes screened for retinopathy	Annually
	Have your feet and legs checked	At least annually
	Obtain ongoing, individual dietary advice	Ongoing, from dietician or other healthcare professional
	If you smoke, obtain support to quit	When appropriate
	Obtain emotional and psychological support	Ongoing
	Have the chance to talk about any sexual problems	Ongoing, at any medical appointment
General care	Be offered a local education course	Upon diagnosis or as yearly refresher
	See specialist healthcare professionals	Ongoing
	Receive high-quality care if admitted to a hospital	Ongoing
	Obtain information and specialist care if you are planning to have a baby	Pre-conception
Laboratory	Get your blood glucose levels measured via HbA _{1c} blood test	At least annually
	Have your blood fats measured	Annually
	Have your kidney function monitored	Annual urine and blood test
Vaccine	Get a free flu vaccination	Annually

Kerr et al. Diabet. Med. 35, 498–503 (2018)



TYPE 1 DIABETES: STAGES AND PREVENTION



Review article

Heterogeneity and endotypes in type 1 diabetes mellitus

Maria J. Redondo ¹✉ & Noel G. Morgan ²



Despite major advances over the past decade, prevention and treatment of type 1 diabetes mellitus (T1DM) remain suboptimal, with large and unexplained variations in individual responses to interventions. The current classification schema for diabetes mellitus does not capture the complexity of this disease or guide clinical management effectively. One of the approaches to achieve the goal of applying precision medicine in diabetes mellitus is to identify endotypes (that is, well-defined subtypes) of the disease each of which has a distinct aetiopathogenesis that might be amenable to specific interventions. Here, we describe epidemiological, clinical, genetic, immunological, histological and metabolic differences within T1DM that, together, suggest heterogeneity in its aetiology and pathogenesis. We then present the emerging endotypes and their impact on T1DM prediction, prevention and treatment.



The six endotypes characterising type 1 diabetes

		Endotypes					
		T1DE1	T1DE2	T1DE3	T1DE4	T1DE5	T1DE6
Properties (strength of association marked by +)	Age at onset (pre-pubertal, pubertal, young-adult, adult, senior)	+	++	+++	+++	++++	All-ages, COVID induced
	Genetic (HLA)	++++	+++	+++	++	++	+
	Immunological (number and titer of autoantibodies)	++++	+++	+++	++	++	+
	C-peptide levels (< 0.3, 0.3-0.7, > 0.7 nM/L)	+	++	++	+++	++++	+++
	BMI (overweight, obese)	+	+	++	++++	+++	++
LADA							

Pozzilli et al. Diabetes Metab Res Rev.
2024;e3770.

T1DE1

T1DE2

Age of onset

C-peptide

Body weight

Autoantibodies

Genes

Immune cells

Abbreviations: IAA, insulin
diabetes endotype 2.

Age of onset

C-peptide

Body weight

Autoantibodies

Genes

Immune cells

T1DE6: COVID-19-induced type 1 diabetes.

Variable

Variable—Many patients report recovering C-peptide levels

Many patients report autoantibody negativity. Currently not enough data to contrast with other endotypes

The virus itself is involved in insulinitis. Unknown what immune cells are involved

Age of onset

C-peptide

Body weight

Autoantibodies

Genes

Immune cells

Age of onset

C-peptide

Body weight

Autoantibodies

Genes

Immune cells

Abbreviations: T1DE1, type 1 diabetes endotype 1; T1DE2, type 1 diabetes

Autoantibodies

Genes

Immune cells

Higher

Lower autoantibodies

Likely greater genetic links than T1DE5

Increased macrophage infiltration. Decreased T cell infiltration than T1DE1-2. Less intense immune attack than T1DE3

in T1DE4-5

lower than T1DE1-2

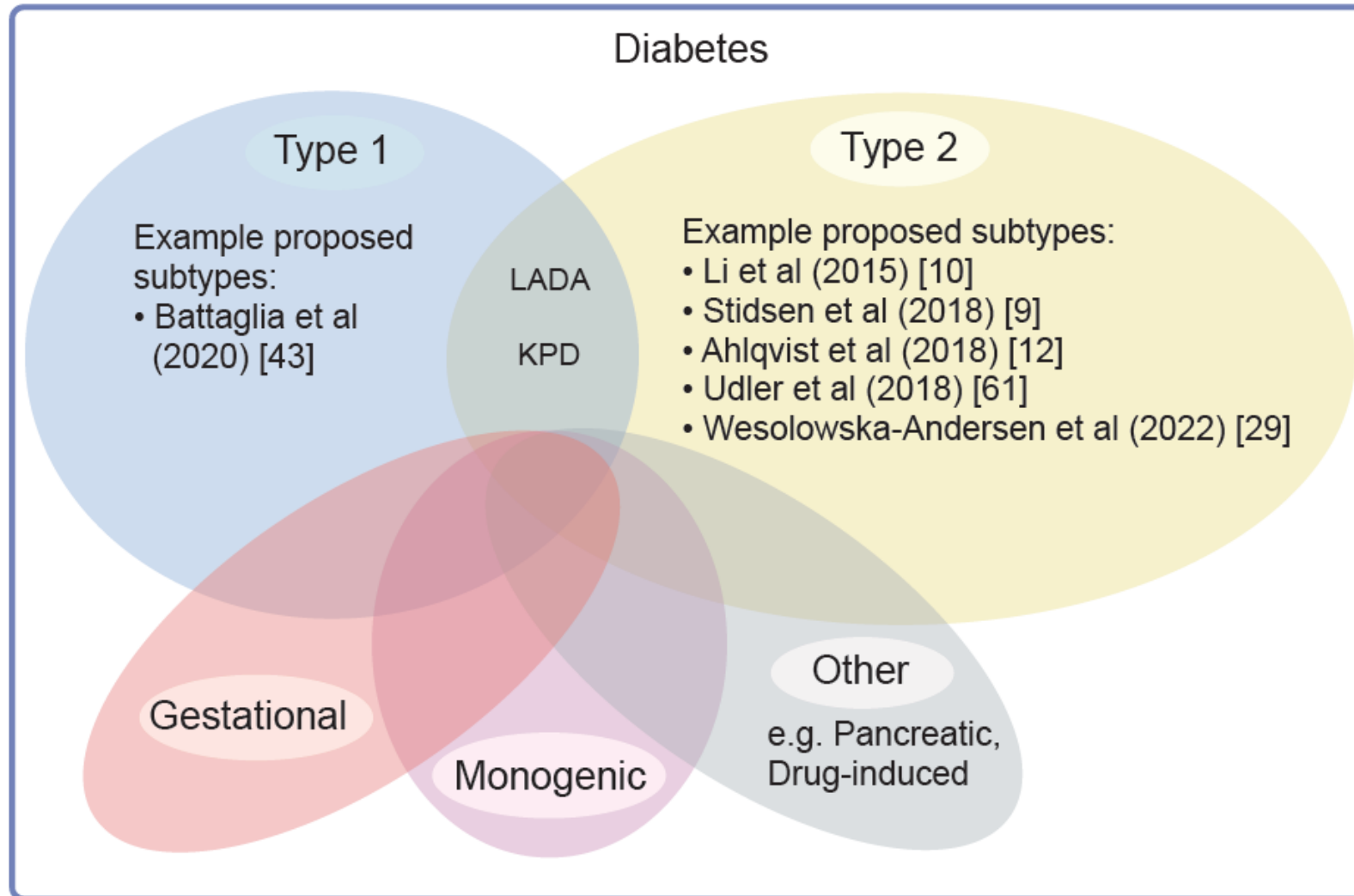
5. Less links than T1DE1-2. Possibly

infiltration than T1DE1-2

T1DE1-3

T1DE1-3

Diabetes subtypes



Deutsch et al (2022) Diabetologia DOI 10.1007/s00125-022-05769-4

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Diabetologia

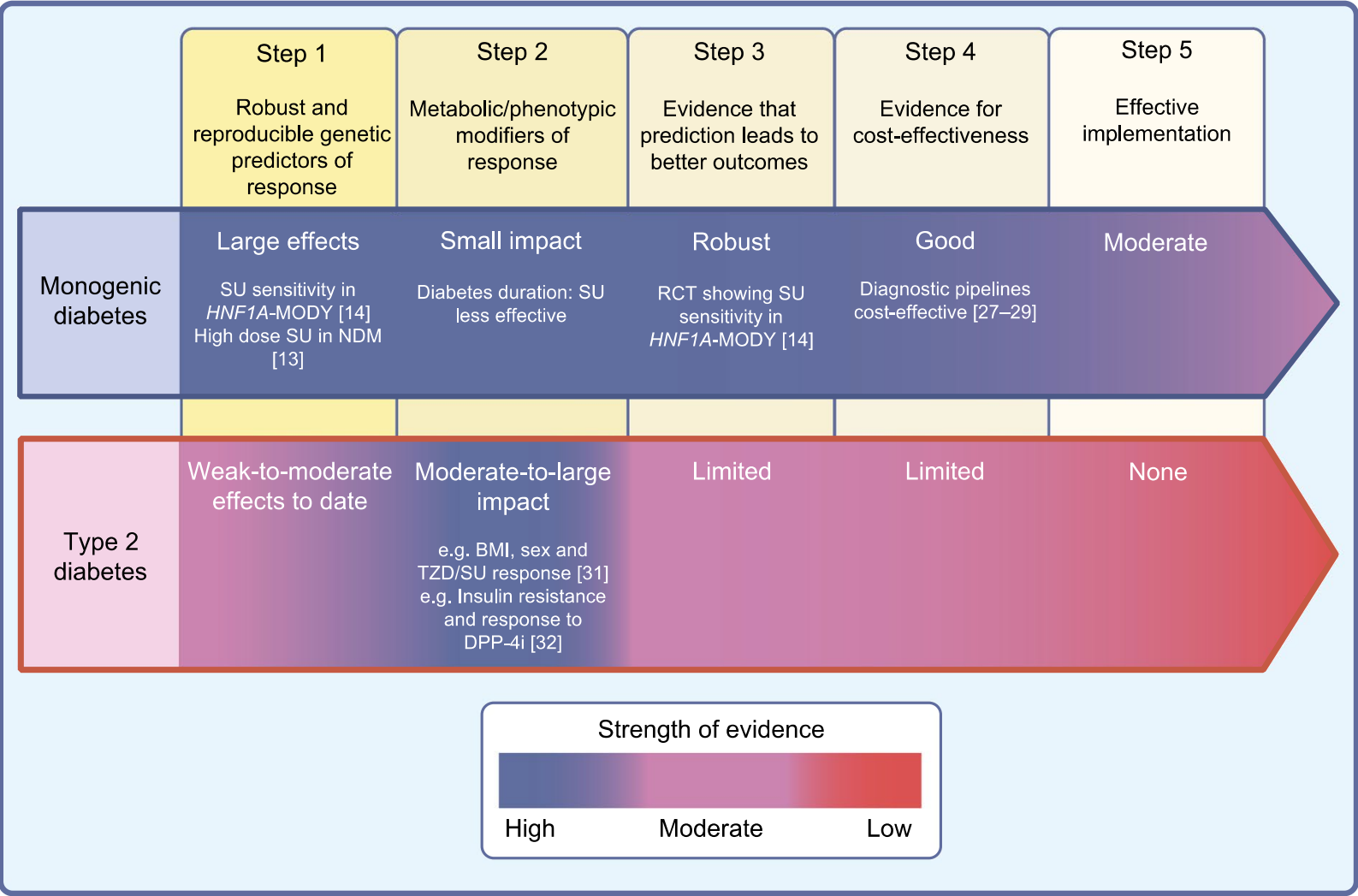


Fig. 1 A roadmap to achieve pharmacological precision medicine in diabetes. Steps 1 to 5 describe the necessary steps for discovery, validation and implementation of precision medicine approaches to the management of diabetes. This is depicted for monogenic diabetes and type 2

diabetes. The colour represents the current strength of evidence, with blue being high and red being low. DPP-4i, DPP-4 inhibitor; NDM, neonatal diabetes mellitus; SU, sulfonylurea; TZD, thiazolidinedione. This figure is available as part of a [downloadable slideset](#)

Phenotypic diabetes subtypes

Severe autoimmune diabetes (SAID): GAD65 positive, low HOMA2-B, lower BMI, higher risk of baseline neuropathy

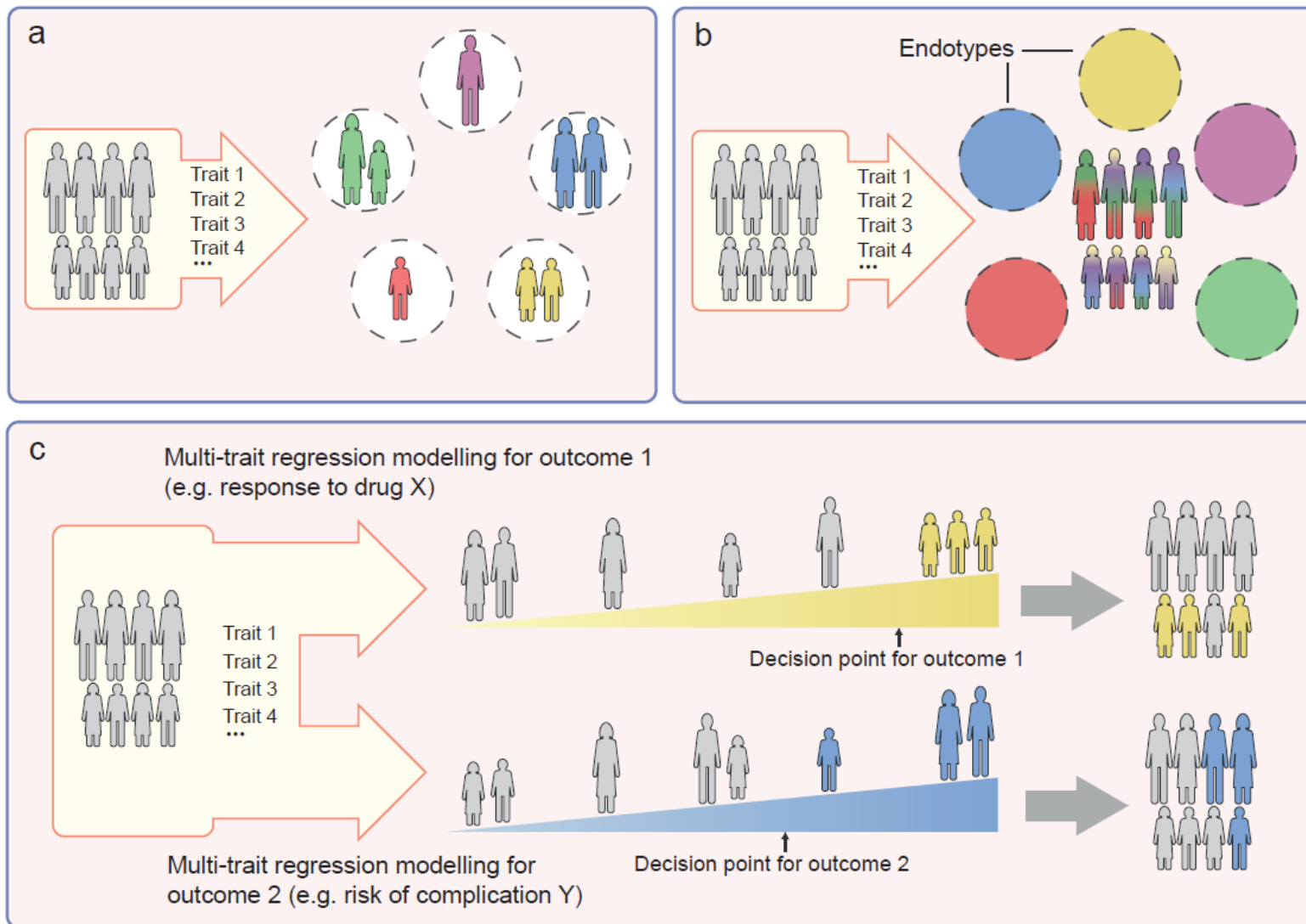
Severe insulin-deficient diabetes (SIDD): Low HOMA2-B, lower BMI, higher risk of retinopathy and neuropathy

Severe insulin-resistant diabetes (SIRD): High HOMA2-B, high HOMA2-IR, high BMI, late onset, higher risk of chronic kidney disease

Mild obesity-related diabetes (MOD): High BMI, early onset, less progressive disease

Mild age-related diabetes (MARD): Late onset, less progressive disease

Strategies for identifying diabetes subtypes



Deutsch et al (2022) Diabetologia DOI 10.1007/s00125-022-05769-4

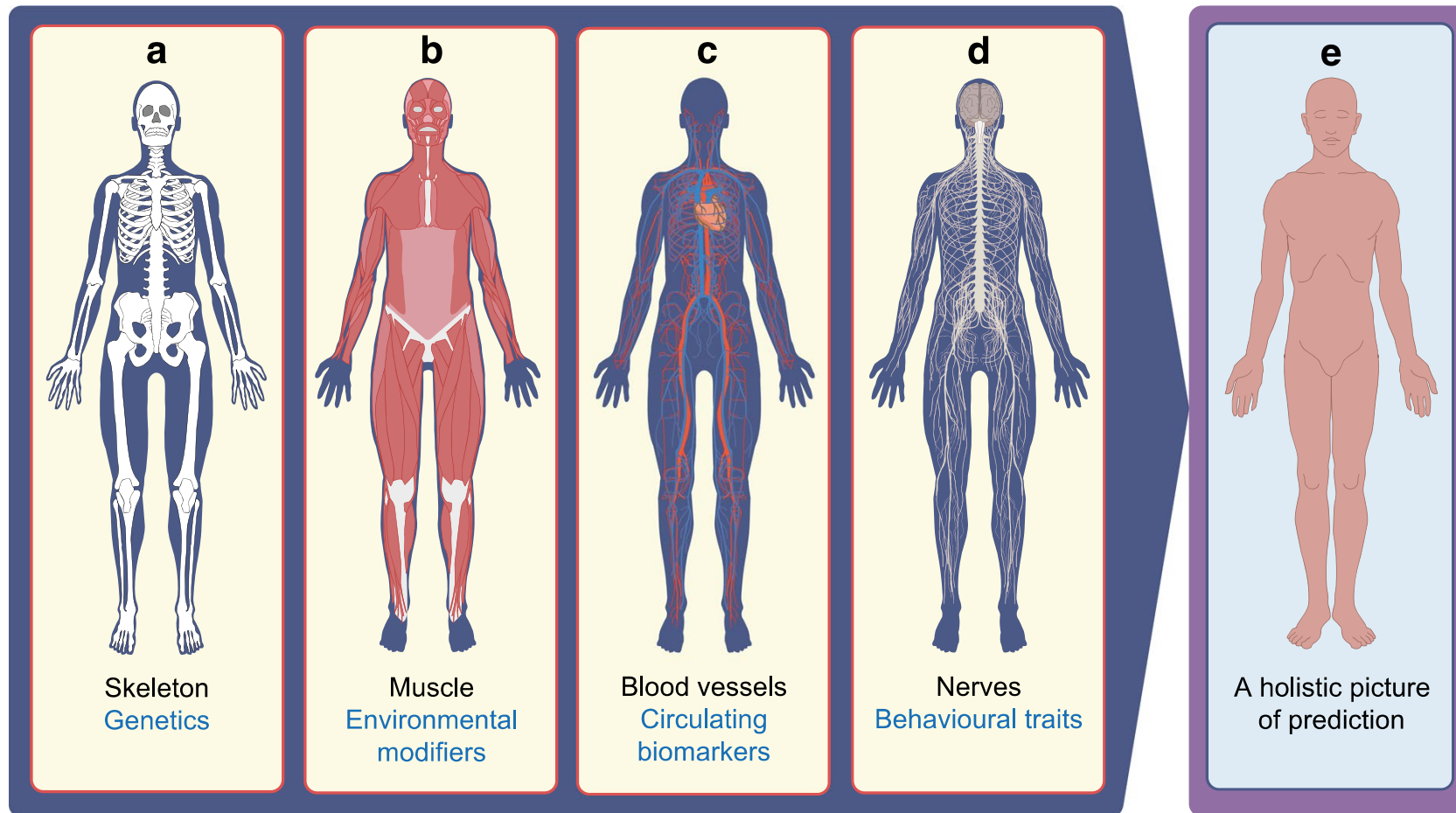
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Diabetologia

Il Genotipo è statico nel tempo e costituisce un ottimo scheletro sul quale agiscono modificatori come i fenotipi e i biomarkers metabolici

Diabetologia (2022) 65:1830–1838



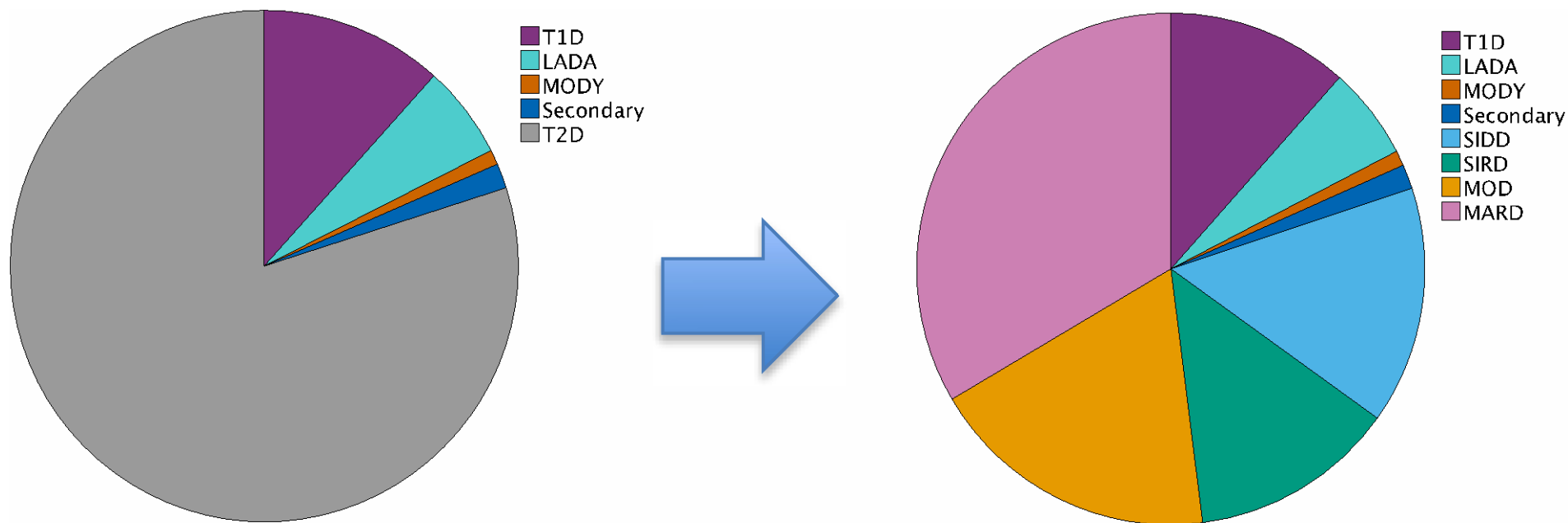


Fig. 1 The spectrum of diabetes subgroups. The data are from the ANDIS project (All New Diabetics in Scania) (<http://is.ludc.med.lu.se>). The criteria used for diagnosis are as follows: T1D: age at onset < 35 years, C-peptide < 0.2 nmol L⁻¹ and GAD antibodies > 20; T1D with relative insulin deficiency if C-peptide 0.2–0.6 nmol L⁻¹. T2D: age at onset > 35 years, C-peptide > 0.6 nmol L⁻¹, GAD antibodies < 10; T2D with relative insulin deficiency C-peptide 0.2–0.6 nmol L⁻¹. LADA (latent autoimmune diabetes in adults): age at onset > 35 years, GAD antibodies > 20; LADA light if GAD antibodies 10–20. The data clearly illustrate the difficulty classifying diabetic patients at diagnosis with 19% unclassifiable (adapted from Endocrinology: Diabetes, Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention, and Treatment: Chapter 6. Genetics of diabetes and diabetic complications. Springer publications 2018).

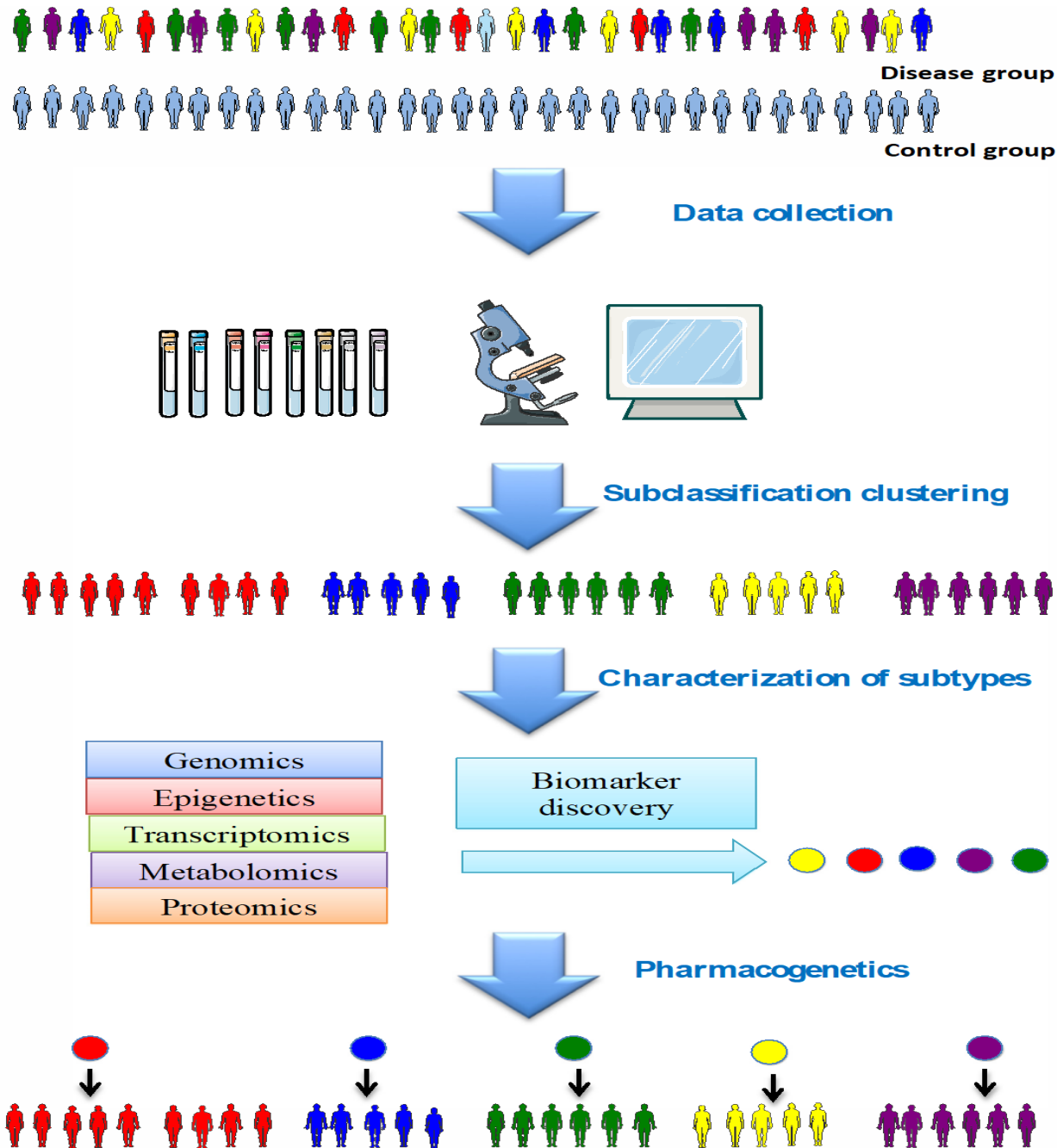
Table 1 Metabolic characteristics and diabetes-related complications of individuals in the novel diabetes subgroups

Diabetes subgroup	Metabolic characteristics	Diabetes-related complications
SAID	Early-onset diabetes	Ketoacidosis at diagnosis [6]
	Low BMI	High risk of retinopathy [29]
	High HbA _{1c}	High incidence of CKD but dependent on baseline eGFR [28]
	Insulin deficiency	
	Presence of GADA	
SIDD	Early-onset diabetes	Ketoacidosis at diagnosis [6]
	Low BMI	High risk of retinopathy [6]
	High HbA _{1c}	Highest prevalence of DSPN [26]
	Insulin deficiency	Highest prevalence of CAN [26]
	GADA negative	High prevalence of erectile dysfunction [33]
SIRD	Late-onset diabetes	Highest liver fat content, fatty liver index, NAFLD fibrosis score and prevalence of NAFLD [6, 26, 29]
	High BMI	Highest risk for macroalbuminuria, CKD and end-stage renal disease [6, 26, 29]
	Most insulin-resistant	High risk of coronary event and stroke (dependent on age and sex) [6]
	GADA negative	High prevalence of erectile dysfunction [33]
MOD	Early-onset diabetes	Intermediate prevalence and risk of diabetes-related complications [6, 26]
	High BMI	
	Intermediate insulin resistance	
MARD	GADA negative	High risk of coronary events and stroke (dependent on age and sex) [6]
	Late-onset diabetes	
	Low BMI	
	GADA negative	

Table 1 Diabetes clusters, characteristics and outcomes

	Cluster/ characteristics	SAID	SIDD	SIRD	MOD	MARD
Phenotype	HbA1c	High	High	Moderate	Moderate	Moderate
characteristics	Age at onset	Early	Early	Late	Late	Latest
	BMI	Low	Low	High	High (obese)	High
	GADA	+(by definition)	-	-	-	-
	ZnT8A autoantibodies	+(common)	-	-	-	-
	Insulin deficiency	++	++	+-	+-	+-
	Insulin resistance	+	+	+++	+	+
	Ketoadidosis at diagnosis	Frequent	Frequent			
Complications	Complications	Little risk of early development of complications	High risk of retinopathy	High risk of diabetic kidney disease Highest prevalence of nonalcoholic fatty liver disease	Little risk of complications	Little risk of complications
Treatment	Insulin	42% Need Insulin	28% Mis-treated by metformin, need often Insulin	<4% Need treatment which enhances insulin sensitivity	<4% Lifestyle, metformin	<4% Lifestyle, metformin

GADA, glutamic acid decarboxylase autoantibodies; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; ZnT8A antibodies, zinc transporter 8 autoantibodies.



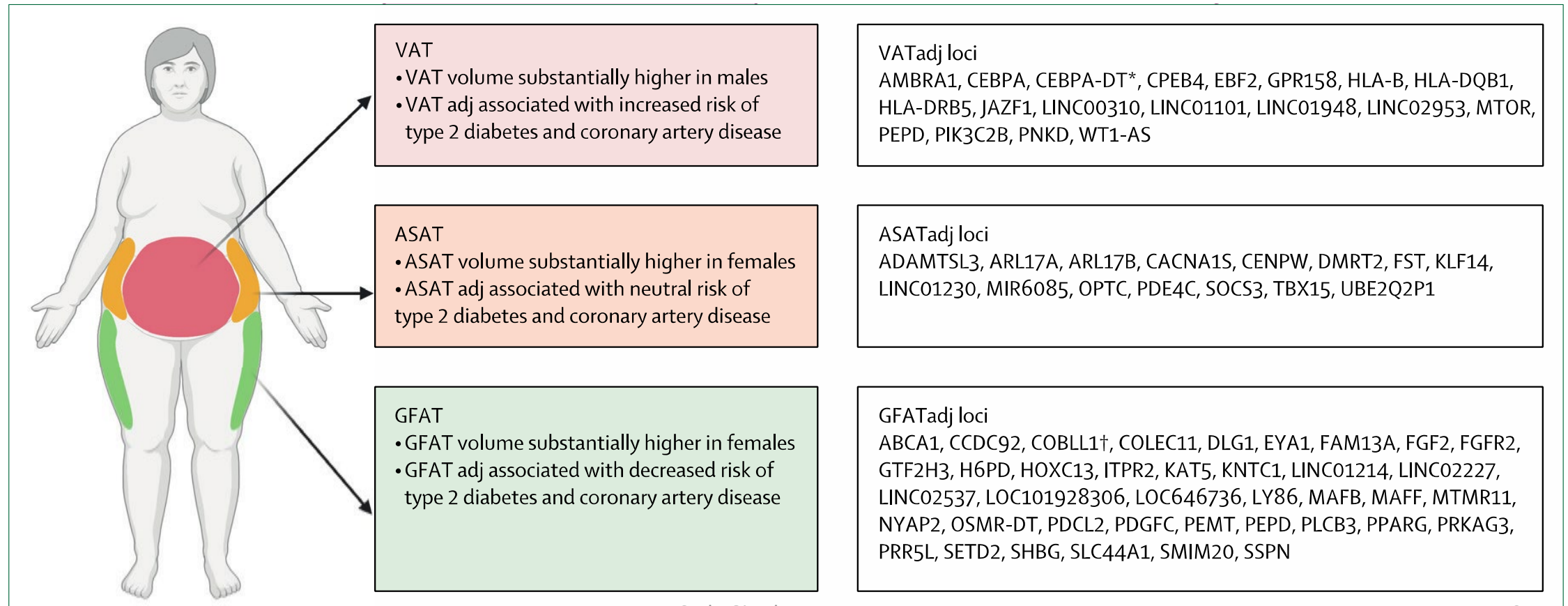
The Association for the Publication of the Journal of Internal Medicine 45
Journal of Internal Medicine, 2019, 285; 40–48

Precision medicine of obesity as an integral part of type 2 diabetes management – past, present, and future

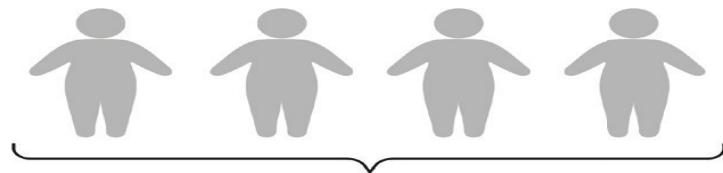
Lukasz Szczerbinski, Jose C Florez

Lancet Diabetes Endocrinol 2023; 11: 861–78

Associations of specific adipose tissue depots with metabolic consequences and distinct genetic loci



Proposed integrated obesity-centred multidisease management algorithm in precision medicine of obesity



ecord data



Novel obesity classification and targeted therapies based on underlying mechanisms of weight gain

	Hungry brain 	Emotional hunger 	Hungry gut 	Slow burn 
Main obesity phenotype	Abnormal satiation*	Abnormal hedonic eating†	Abnormal satiety‡	Low predicted energy expenditure
Features (compared with a non-phenotype group)	• Consume 62% more calories before reaching fullness	• 2-3 times higher anxiety levels	• 31% faster gastric emptying rate	• 12% lower predicted resting energy expenditure • Reduced muscle mass • Less active
Proposed targeted LIFESTYLE therapy	• Time-restricted eating	• Low-calorie diet with intensive behavioural group therapy	• Low-calorie diet with pre-meal protein supplements	• Low-calorie diet with post-workout protein supplementation and high-intensity interval training
Proposed targeted PHARMACOTHERAPY	• Phentermine plus topiramate extended release	• Oral naltrexone plus bupropion sustained release	• Liraglutide	• Phentermine

PREVALENZA

16%

12%

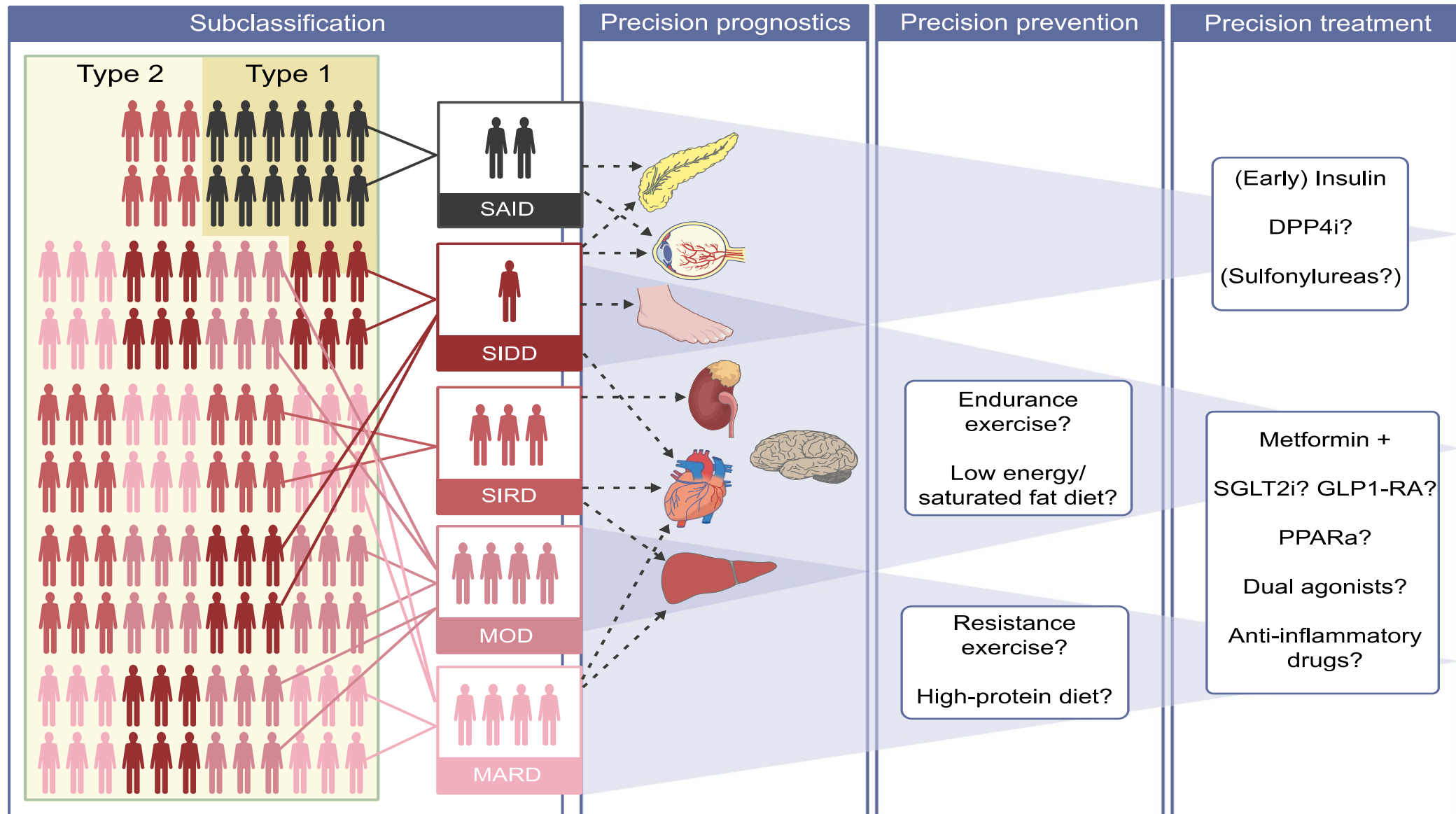
18%

12%

**combinati 27%
negativi 15%**

**Precision medicine
aims to tailor
treatment to an
individual based on
their clinical
characteristics**

Precision Diabetology



Integrating artificial intelligence into the diabetes care continuum

Bin Sheng*, Krithi Pushpanathan*, Zhouyu Guan*, Quan Hziung Lim*, Zhi Wei Lim, Samantha Min Er Yew, Jocelyn Hui Lin Goh, Yong Mong Bee, Charumathi Sabanayagam, Nick Sevdalis, Cynthia Ciwei Lim, Chwee Teck Lim, Jonathan Shaw, Weiping Jia, Elif Ilhan Ekinci, Rafael Simó, Lee-Ling Lim†, Huating Li†, Yih-Chung Tham†

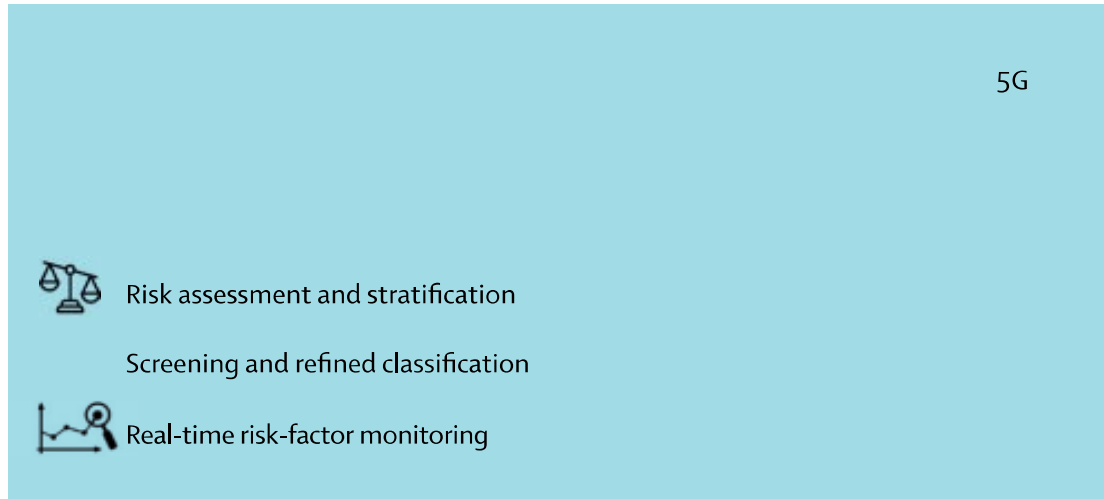
Proactive health promotion and
empowerment for self-care

Treatment optimisation of complex diabetes
Specialised management of
complex diabetes

Tertiary care
Advanced care for
diabetes-related complications



Integrating artificial intelligence into the diabetes care continuum



mobile network. network. *exdez/Getty Images.

†Osaka Wayne Studios/Getty Images. ‡Eduard Muzhevskiy/Science Photo Library. §Sarayut Thaneerat/Getty Images.

ORIGINAL ARTICLE

Population-Level Prediction of 1
 From Claims Data and Analysis

Narges Razavian¹ Saul Blacker² Ann Marie Schmidt³ Aaron Smith¹
 Diabetes Care

Research Collaboration to Use Big
 Data for Diabetes Prevention

Researchers in Indiana will leverage big data analytics techniques to explore the prevention and treatment of type 2 diabetes.

Machine Learning for
 Diabetes Mellitus dur
 in Non-Diabetic Patie



Praveen Gopal Chait^{1,2} Suresh Woon Bha² Sri
 The NEW ENGL

Machine Learning to Predict the
 Risk of Incident Heart Failure
 Hospitalization Among Patients
 With Diabetes: The WATCH-DM
 Risk Score

MEDICINE AND SOCIETY



Matthew W. Segar,¹
 Muthiah Vaduganathan,²
 Kershaw V. Patel,¹ Darren K. McGuire,¹
 Javed Butler,³ Gregg C. Fonarow,⁴
 Mujeeb Basit,¹ Vaishnavi Kannan,⁵
 Justin L. Grodin,¹ Brendan Everett,²
 Duwayne Willett,¹ Jarett Berry,¹ and
 Ambarish Pandey¹

Artificial intelligence in diabetes care

Debra Malin

Digital Futures Past — The L

V. Buch¹ , G. Varughese² and M. Maruthappu¹

Jeremy A. Greene, M.D., Ph

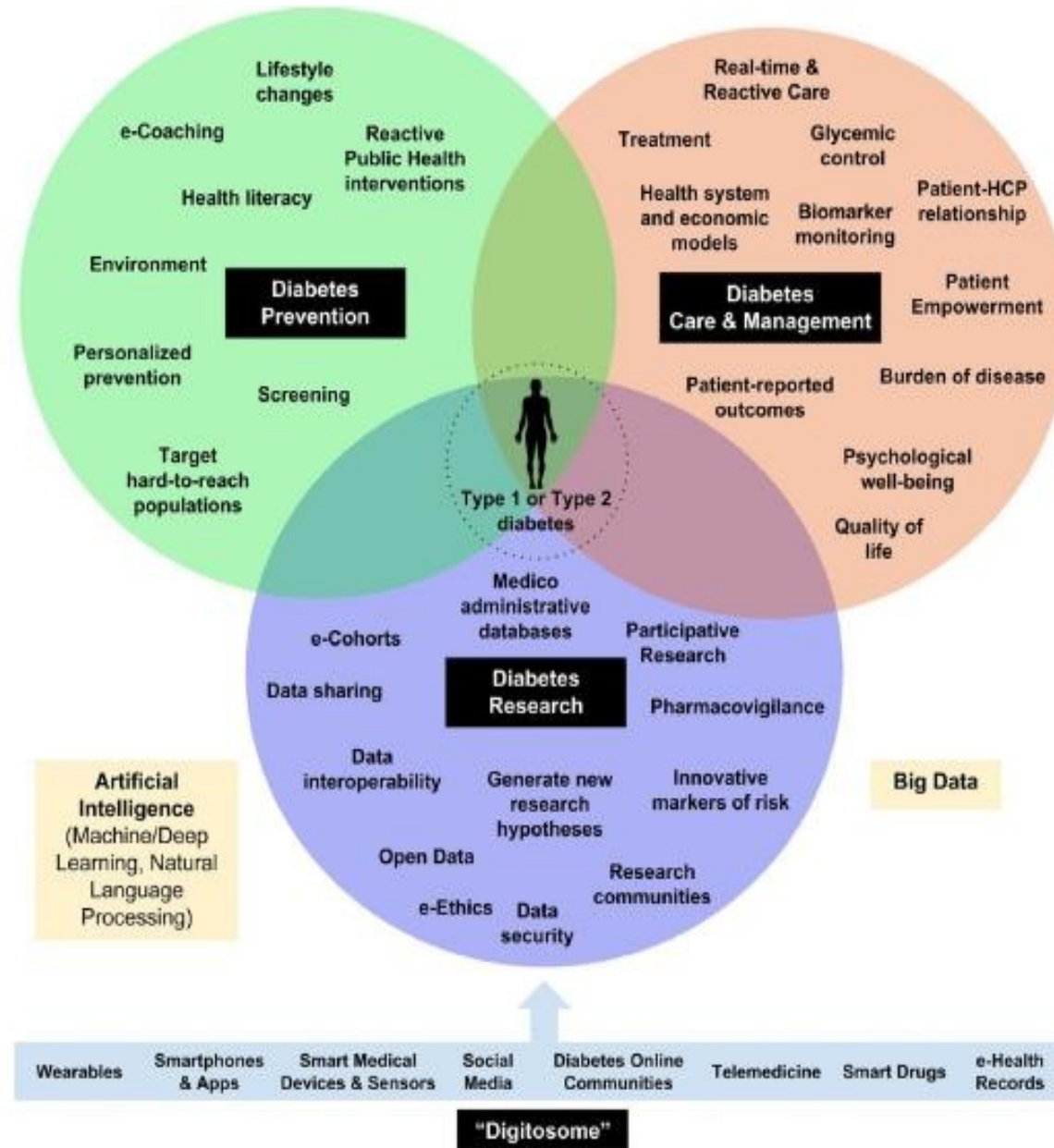
¹ Care Cure, London and ² University Hospitals of North Midlands, Stoke-On-Trent, UK

Digital diabetes: Perspectives for diabetes prevention, management and research

G. Fagherazzi^{a,*}, P. Rava^b

^aInserm UMR1018, Paris South, Paris Saclay

^bInserm UMR1153, Paris Descartes Univer.



Queste tecniche di analisi predittiva, applicate allo studio del diabete, consentono di:

- ✓ Predire la comparsa di diabete
- ✓ Individuare nuovi fattori di rischio e la sottopopolazione più a rischio di svilupparlo
- ✓ Predire l'insorgenza e l'evoluzione delle complicanze
- ✓ Individuare il tipo di trattamento più efficace a seconda del sottogruppo di popolazione e a seconda del momento di comparsa della malattia
- ✓ Diagnosi automatizzata
- ✓ Individuare quali pazienti richiedono più attenzione
- ✓ Individuare quali strategie sono più efficaci a seconda del paziente



Modalità più efficienti di cura della persona, con costi minori e con migliori outcomes

L'aumento di complessità, ben gestito, consentirà al medico di poter prendere decisioni migliori



Transforming Diabetes Care Through Artificial Intelligence: The Future Is Here

Grazie



Carla Giordano, MD



1) Identification of Key Patient-Level Markers for Enhanced Precision in Diabetes Medicine

2) Prioritization of Outcomes and Clarity in the Definition(s) of Success in Diabetes Therapy or Other Health Interventions for Individuals With Diabetes

3) Opportunities for Genetic Data to Improve Clinical Care for Diabetes

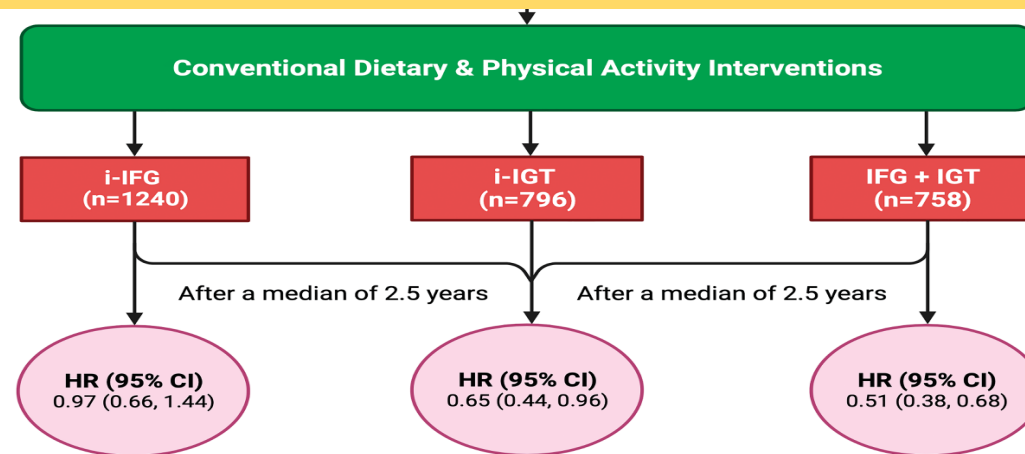
4) Collection and Use of New Multisource Data

5) Emphasis on Clinical Utility

Effect of Conventional Lifestyle Interventions on Type 2 Diabetes Incidence by Glucose-Defined Prediabetes Phenotype: An Individual Participant Data Meta-analysis of Randomized Controlled Trials

ARTICLE HIGHLIGHTS

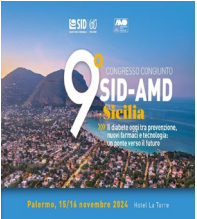
- We undertook this study because it is unclear whether conventional lifestyle interventions could reduce diabetes incidence in all three glucose-defined prediabetes phenotypes.
- We specifically sought to answer the question of whether the effect of conventional lifestyle interventions on diabetes incidence differs by prediabetes phenotype.
- We found that diabetes incidence was reduced significantly in individuals with impaired glucose tolerance (with or without impaired fasting glucose) but not in those with isolated impaired fasting glucose.
- The implications of our findings are that there is a need for precision prevention of type 2 diabetes.



HR, hazard ratio; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; IFG + IGT, impaired fasting glucose plus impaired glucose tolerance.

Gaps in the current knowledge, open questions and future research directions

- The proposed novel diabetes subgroups [6] are partly based on fasting C-peptide, which is not always available, so the selection of clustering variables should be optimised to ensure simple and reproducible clinical measures
- The original cluster algorithm assessed autoimmunity only by measuring GADA [6]; adding other islet-directed antibodies will expand the subgroup with autoimmune diabetes [26]
- Some people with diabetes migrate between diabetes subgroups over time [26, 38]. More studies investigating this phenomenon and linking it to disease progression are warranted to assess the stability of subgroup allocation and its impact on the utility of this concept
- Different strategies have been proposed to reclassify diabetes [58, 59]. Future studies should compare the clinical utility of distinct diabetes subgroups and probabilistic models using continuous risk factors for the prediction of complications and treatment response. Irrespective of the underlying statistical method, the practicability in clinical care of different treatment decisions depending on reclassification needs to be proven
- Both phenotypic and genotypic data could be used to reclassify diabetes [6, 22]. Given the wide age range of diabetes onset across the lifespan both approaches may be complementary but with different relative contributions to risk prediction depending on age
- Biomarker studies (e.g. on biomarkers of inflammation) point towards pathomechanisms that differ between diabetes subgroups [43, 46, 47]. An extension of phenotyping including not only multiple omics data (e.g. genomics, metabolomics, proteomics, transcriptomics) but also deep molecular and physiological phenotyping using wearable devices may help to provide further insight and to refine the subtyping of diabetes [10, 60-62]
- Individual responses to diet and exercise vary between individuals [63, 64]. It is not known to what extent this individuality is also related to different pathomechanisms that characterise the novel diabetes subgroups
- The five diabetes subgroups were developed using data from European cohorts [6] but diabetes phenotypes and drug responses can differ between ethnic groups [59, 65, 66]. Replication studies in non-White people with diabetes identified additional subgroups but were often based on different sets of clustering variables and/or diabetes durations [27, 29, 30, 36, 38-41]. Overall, the applicability of the subgroup concept in the general population and in different ethnic groups requires further study
- Studies have focused so far on associations between diabetes subgroups and objective clinical measures but also need to take into account patient-centred mental health and quality-of-life outcomes [13]
- Given the novel findings on subgroups with different risk trajectories among people with and without diabetes [6, 23], future investigations should assess whether individuals in these subgroups require not only different intensities in drug treatment or lifestyle intervention programmes but also different intervals in screening and monitoring for complications
- If it becomes a requirement for the approval of new drugs to demonstrate whether they are equally effective in different subgroups or just recommended for specific subgroups, smaller market shares for precision medicines may entail challenges for future drug development [67]



1) highlighting the research and clinical domains of interest in precision diabetes medicine (diagnosis, prevention, treatment, prognosis, and monitoring); 2) engaging with key stakeholders in areas germane to precision diabetes medicine, including clinicians, researchers in academia and industry, and those working with health care data science and informatics, health policy and reform, and social sciences; 3) identifying the gaps and future steps toward the clinical application of precision medicine; and 4) establishing a dialogue with people with diabetes to keep lived experiences and unmet needs at the forefront of the vision for precision diabetes medicine.

Key points

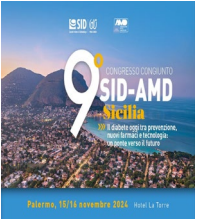
- Type 1 diabetes mellitus (T1DM) is heterogeneous; defining endotypes, or disease subtypes each of which has a unique aetiopathogenesis that is amenable to a particular intervention, will help apply precision medicine to T1DM.
- T1DM endotype 1 (T1DE1) includes T1DM diagnosed in early childhood and is characterized by extensive, early, β -cell destruction, aggressive insulitis with abundant CD8⁺ T and CD20⁺ B cells, aberrant proinsulin processing and an elevated circulating proinsulin to C-peptide ratio.
- T1DM endotype 2 (T1DE2) includes T1DM diagnosed in adolescence or adulthood and is characterized by retention of many residual insulin-containing islets and without insulitis, fewer infiltrating CD8⁺ T cells, few CD20⁺ B cells, normal proinsulin processing and lower proinsulin to C-peptide ratio than T1DE2.
- Evidence is emerging that T1DE1 might respond better than T1DE2 to interventional immunotherapy with agents targeted to specific immune cell subsets, such as rituximab or teplizumab, while GAD-alum therapy might be effective for treating T1DE2.
- The T1DE2 endotype could underlie a spectrum of phenotypes with different degrees of severity of the autoimmune attack and thus, different rates of progression to insulin dependence, ranging from classic T1DM to latent autoimmune diabetes mellitus in adults or slowly progressive insulin-dependent diabetes mellitus.



Questi strumenti riescono

- ...ad estrarre dati coerenti...
- ...a fornire AL MEDICO elementi per prendere decisioni...
- ...a dare NON un risultato certo ma formidabili indicazioni...
- ...ad elaborare direttamente i dati (tirano fuori «conoscenza nascosta»)...
- ...ad analizzare diverse banche dati...

Endotype	T1DE1	T1DE2
Primary genetic association	HLA DR4-DQ8	HLA DR3-DQ2
Islet autoantibodies	IAA first (<2 years old), then IA-2 with or without GAD65 autoantibodies High percentage IAA+ and IAA titres at T1DM onset	GAD autoantibodies first, then with or without other autoantibodies
Other immunological findings	High percentage of islet-infiltrating CD8 ⁺ T cells, high percentage of CD20 ⁺ B cells	Low percentage of CD8 ⁺ T cells compared with T1DE1, very low percentage of CD20 ⁺ B cells compared with T1DE1
β-Cell abnormalities	High proinsulin to C-peptide ratio Low percentage of insulin-containing cells Abnormal β-cell maturation	Higher percentage of insulin-containing islets compared with T1DE1
Response to immunomodulators	Yes	Less responsive than T1DE1
Other disease associations	Coeliac disease	Thyroid autoimmunity



1) highlighting the research and clinical domains of interest in precision diabetes medicine (diagnosis, prevention, treatment, prognosis, and monitoring); 2) engaging with key stakeholders in areas germane to precision diabetes medicine, including clinicians, researchers in academia and industry, and those working with health care data science and informatics, health policy and reform, and social sciences; 3) identifying the gaps and future steps toward the clinical application of precision medicine; and 4) establishing a dialogue with people with diabetes to keep lived experiences and unmet needs at the forefront of the vision for precision diabetes medicine.

Table 2 Overview of clustering studies using alternative demographic and clinical variables to identify subgroups of diabetes

Cohort characteristic	Clustering variables	Subgroups	Specific findings
VNDS, Italy (739 with T2D)	Age, BMI, HOMA-2 estimates of beta cell function and insulin resistance	SIDD MARD OIRD EOD	Replication of SIDD and MARD OIRD comprising MOD and SIRD MARD associated with CVD Highest HbA _{1c} after 14-month follow-up in SIDD
Three cohort studies from Europe: Hoorn DCS; GoDARTS; ANDIS (15,940 people with T2D, within 2 years of diagnosis)	Age, BMI, HbA _{1c} , random or fasting C-peptide, HDL-cholesterol	Five distinct T2D subgroups	Three subgroups could be mapped back to the original ANDIS clusters (SIDD, SIRD, MOD) Two subgroups (MD and MDH related to MARD) Progression to insulin fastest for SIDD and slowest for MDH
MASALA and MESA multi-ethnic cohorts from USA (1293 people with diabetes; mean diabetes duration 5.7 years)	Age at diagnosis, BMI HbA _{1c} , HOMA estimates of beta cell function and insulin resistance	Five T2D subgroups: older age, severe hyperglycaemia, severe obesity, younger age at onset; requiring insulin medication use	Older age most common subgroup for all race/ethnicities apart from South Asians Severe hyperglycaemia subgroup most frequent in South Asians Risk for renal complications and subclinical CVD differed by subgroup and by race/ethnicity
Look AHEAD (5145 overweight/obese people with T2D and 10 years of lifestyle intervention or control group)	Age at diagnosis, BMI, WC, HbA _{1c}	Four subgroups: by older age at diabetes onset; poor glucose control; severe obesity; younger age at diabetes onset	Interaction between lifestyle intervention and diabetes subgroups for three composite cardiovascular outcomes Increased cardiovascular risk for people in subgroup with poor glucose control randomised to lifestyle intervention

Diabetes 2030: routine care

Diabetes care in the future is very likely to be a **hybrid system** between humans (multidisciplinary professional teams and people with diabetes) and machines (medical devices and consumer products). Major therapy changes will still be made during human-to-human interactions, but in between visits, much of routine care will be delivered by technologies that fulfil the following tasks.

Digital diabetes ecosystem

A **'digital diabetes ecosystem'** combines the Internet of Medical Things, personal health sensor data, and the use of artificial intelligence and machine learning with smart-phones providing continuous access to the Internet.

Table 2 (continued)

Cohort characteristic	Clustering variables	Subgroups	Specific findings
NHANES (USA) and four Mexican cohorts (1758 people with T2D in NHANES; 9887 people with T2D in the open-population Mexican cohorts)	Models based on different combinations of years since diagnosis, BMI, HbA _{1c} , HOMA-2 estimates of beta cell function and insulin resistance, fasting plasma glucose, METS-IR, METS-VF, age at diabetes onset	Four subgroups: obesity-related; insulin-deficient; insulin-resistant; age-related	Risk of retinopathy highest for insulin-deficient subgroup and lowest for obesity-related subgroup Subgroup transitions observed after 3 months, 1 year and 2 years
Thirteen cohort studies from nine countries in Latin America and the Caribbean (8361 people with T2D)	Age, sex, BMI, WC, systolic/diastolic BP, T2D family history	Four clusters: Cluster 0, highest BP; Cluster 1, highest BMI and WC, highest proportion of positive family history of diabetes; Cluster 2, most beneficial risk profile; Cluster 3, highest age	Heterogeneous distribution of clusters across countries
Electronic medical records of a tertiary diabetes centre, India (19,804 people with T2D; diabetes duration <5 years)	Age at diagnosis, BMI, WC, HbA _{1c} , triacylglycerols, HDL-cholesterol, C-peptide (fasting and stimulated)	Four clusters: Cluster 1, SIDD; Cluster 2, IROD; Cluster 3, CIRDD; Cluster 4, MARD	SIDD and MARD similar to diabetes subgroups in other populations IROD and CIRDD unique to Asian Indian population IROD showed highest BMI and highest C-peptide levels CIRDD showed lowest age of onset, highest serum triacylglycerols, highest risk for kidney disease
Retrospective clinic-based study sample, PR China (5414 people with T2D; mean diabetes duration 8.6 years)	Age at diagnosis, BMI, HbA _{1c} , HOMA-2 estimates of beta cell function and insulin resistance, GADA; additional model with triacylglycerols and uric acid	Replication of SAID, SIRD and MARD when using the original six clustering variables Replication of SAID, SIDD, SIRD, MOD and MARD and identification of novel subgroups (UARD, IRD) when all clustering variables were used	Higher risk for retinopathy, peripheral neuropathy, hypertension and CKD for SIRD (vs IRD) Higher risk for retinopathy and diabetic foot for SIDD (vs IRD)

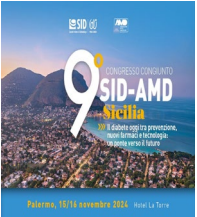
Table 2 (continued)

Cohort characteristic	Clustering variables	Subgroups	Specific findings
Three global cardiovascular outcomes trials: DEVOTE, LEADER, SUSTAIN-6 (20,274 people with T2D; follow-up of 2.0–3.8 years)	Age at diagnosis, BMI, HbA _{1c}	Identification of four subgroups: clusters A–D	Differences between clusters for major adverse cardiovascular events, cardiovascular death, nephropathy and severe hypoglycaemia when comparing subgroups in at least one cohort

Table 3 Novel diabetes subgroups: glucose-lowering therapy in cohort studies and response to therapy in ADOPT

Diabetes subgroup	Therapy in cohort studies	Response to therapy in ADOPT	Comment
SAID	Most frequent use of insulin and lowest use of metformin at baseline [6, 29] Shortest time to sustained insulin use [6]	Not analysed in the context of novel diabetes subgroups	Findings are in line with the established treatment for type 1 diabetes and LADA
SIDD	Most frequent use of metformin at baseline [8, 29] Frequent use of insulin at baseline and short time to sustained insulin use, although less pronounced than for SAID [6] Shortest time to treatment with oral medication other than metformin and longest time to reach HbA _{1c} treatment goal [6]	Initial treatment response best with sulfonylureas but highest HbA _{1c} increase thereafter with sulfonylureas	Data are in line with the low beta cell reserves in this subgroup
SIRD	Most frequently treated with metformin or without glucose-lowering therapy [6] Evidence for higher insulin use later after diabetes diagnosis [29]	HbA _{1c} benefit with thiazolidinedione therapy	Findings are plausible given the pronounced insulin resistance and high prevalence of NAFLD in SIRD
MOD	Most frequently treated with metformin or without glucose-lowering therapy [6] Lowest baseline use of insulin [29]	Initial treatment response best with sulfonylureas but highest HbA _{1c} increase thereafter with sulfonylureas	Data indicate a mild form and mild progression of diabetes
MARD	Most frequently treated with metformin or without glucose-lowering therapy [6] Low cumulative incidence of treatment with oral medication other than metformin or of sustained insulin use [6]	HbA _{1c} benefit with sulfonylurea therapy, limited to about 2 years, vs metformin and thiazolidinedione treatment	Data indicate a mild form and mild progression of diabetes

Precision medicine aims to treat an individual based on their clinical characteristics. A differential drug response, critical to using these features for therapy selection, has never been examined directly in type 2 diabetes. We tested two hypotheses: 1) individuals with $\text{BMI} > 30 \text{ kg/m}^2$, compared with $\text{BMI} \leq 30 \text{ kg/m}^2$, have greater glucose lowering with thiazolidinediones than DPP4-inhibitors, and 2) individuals with $\text{eGFR } 60\text{--}90 \text{ ml/min/1.73m}^2$ compared with $\text{eGFR} > 90 \text{ ml/min/1.73m}^2$ have greater glucose lowering with DPP4-inhibitors than SGLT2-inhibitors. The primary endpoint for both hypotheses was the achieved HbA1c difference between strata for the two drugs. 525 people with type 2 diabetes participated in a UK based randomised, double-blind, three-way crossover trial of 16 weeks treatment with each of sitagliptin 100mg/day, canagliflozin 100mg/day and pioglitazone 30mg/day added to metformin alone or metformin plus sulfonylurea. Overall, the achieved HbA1c was similar for the three drugs pioglitazone 59.6 mmol/mol, sitagliptin 60.0 mmol/mol, canagliflozin 60.6 mmol/mol ($p=0.2$). Participants with $\text{BMI} > 30 \text{ kg/m}^2$, compared with $\text{BMI} \leq 30 \text{ kg/m}^2$, had a 2.88 mmol/mol (95% CI 0.98, 4.79) lower HbA1c on pioglitazone than on sitagliptin ($n=356$, $P=0.003$). Participants with $\text{eGFR } 60\text{--}90 \text{ ml/min/1.73m}^2$, compared with $\text{eGFR} > 90 \text{ ml/min/1.73m}^2$, had a 2.90 mmol/mol (95% CI 1.19, 4.61) lower HbA1c on sitagliptin than on canagliflozin ($n=342$, $P=0.001$). There were 2201 adverse events reported, and 447/525 (85%) randomised participants experienced an adverse event on at least one of the study drugs. In this precision medicine trial in type 2 diabetes, our findings support the use of simple routinely available clinical measures to identify the drug class most likely to deliver the greatest glycaemic reduction for a given patient. ClinicalTrials.gov registration: NCT02653209; ISRCTN registration 12039221..



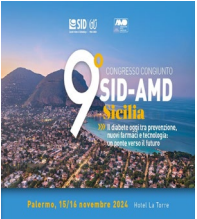
AI in screening, detecting, and predicting diabetes

Title		Number of participants	AI method or solution	Data sources and input variables	Key findings
Screening and detection of diabetes					
Shu et al (2017) ⁴¹	An extensive analysis of various texture feature extractors to detect diabetes mellitus using facial specific regions	515	Support vector machines	Texture features extracted from facial-specific regions among Chinese participants (231 without diabetes and 284 with diabetes)	Accuracy 0.990
Li et al (2021) ⁴²	A tongue features fusion approach to predicting prediabetes and diabetes with machine learning	1710	Genetic algorithm and extreme gradient boosting model	Tongue features among Chinese participants (570 healthy control individuals, 570 with prediabetes, and 570 with diabetes)	AUROC 0.924; accuracy 0.821
Zhang et al (2021) ⁴³	Deep-learning models for the detection and incidence prediction of chronic kidney disease and type 2 diabetes from retinal fundus images	Training on 34 429 participants (68 858 images); internal validation on 8727 participants (17 454 images); external validation on 11 140 participants (22 280 images)	ResNet-50 convolutional neural network	Retinal fundus images from three independent datasets of Chinese participants (37 846 without diabetes and 16 450 with type 2 diabetes)	Internal validation AUROC 0.923 (95% CI 0.913–0.932); external validation a range of AUROCs from 0.820 to 0.854
Avram et al (2020) ⁴⁴	A digital biomarker of diabetes from smartphone-based vascular signals	Primary cohort 53 870; contemporary cohort 7806; clinic cohort 181	Convolutional neural networks	Photoplethysmography recordings from Health eHeart Study participants and patients referred to cardiovascular-prevention clinics	Primary cohort AUROC 0.766 (95% CI 0.750–0.782); contemporary cohort 0.740 (0.723–0.758); clinic cohort 0.682 (0.605–0.755)
Zhang et al (2023) ⁴⁵	Noninvasive and affordable type 2 diabetes screening by deep learning-based risk assessment and detection using ophthalmic images inspired by traditional Chinese medicine	Training on 67 151 participants (416 580 images); internal validation on 8876 participants (62 761 images); external validation on 3668 participants (28 661 images)	ResNet-18 convolutional neural network	External eye photos from four independent datasets of Chinese participants (70 479 healthy control individuals, 327 with prediabetes, and 8889 with type 2 diabetes)	Internal validation AUROC 0.696 (95% CI 0.681–0.712); external validation a range of AUROCs from 0.712 to 0.796

AI in screening, detecting, and predicting diabetes

Prediction of diabetes onset					
Choi et al (2019) ⁴⁶	Machine learning for the prediction of new-onset diabetes mellitus during 5-year follow-up in non-diabetic patients with cardiovascular risks	8454	Logistic regression	Demographic characteristics, BMI, medical history, blood-test results, and cardiovascular and diabetes medications of individuals without a history of diabetes at the Cardiovascular Center of Korea University Guro Hospital (Seoul, South Korea)	AUROC 0.78
Nomura et al (2020) ⁴⁷	SAT-LB121 development of a machine-learning method for predicting new onset of diabetes mellitus: a retrospective analysis of 509 153 annual specific health checkup records	65 505	Gradient boosting	Nationwide health-checkup data (ie, physical examinations, blood and urine tests, and participant questionnaires) of participants without diabetes at baseline from Kanazawa, Japan	AUROC 0.71 (95% CI 0.69–0.72)
Ravaut et al (2021) ⁴⁸	Development and validation of a machine learning model using administrative health data to predict onset of type 2 diabetes	2 137 343	Gradient boosting	>300 features based on demographic characteristics, geographical information, chronic conditions, and history of health-care use of a random sample of residents without type 2 diabetes from all cities in Ontario, Canada	AUROC 0.803 (95% CI 0.802–0.803)
Zhang et al (2021) ⁴³	Deep-learning models for the detection and incidence prediction of chronic kidney disease and type 2 diabetes from retinal fundus images	Training on 6807 participants; internal validation on 1778 participants; external validation on 3144 participants	ResNet-50 convolutional neural network	Retinal fundus images and clinical data (eg, age, sex, blood pressure, height, weight, BMI, and hypertension) from two independent datasets of Chinese participants without diabetes at baseline	Internal validation C index 0.781 (95% CI 0.743–0.819); external validation C index 0.765 (0.723–0.799)

Please note that some studies did not provide measures of precision (eg, 95% CI). AI=artificial intelligence. AUROC=area under the receiver operating characteristic curve.



Analysis of type 2 diabetes heterogeneity with a tree-like representation: insights from the prospective German Diabetes Study and the LURIC cohort



Figure 1: Visual representation of phenotypic characteristics on a tree-like graph structure as a result of data dimensionality reduction of nine clinical variables
The DDRTree algorithm was used to reduce nine clinical variables residualised for age and sex into a non-linear tree structure and map individuals from the GDS cohort into the pre-existing tree derived from the Scottish cohort.¹¹ Yellow, blue, and red dots represent examples of key characteristics of individuals positioned in the respective branches of the tree. DDRTree=Data dimensionality reduction Tree. GDS=German Diabetes Study.

Ambito epidemiologico

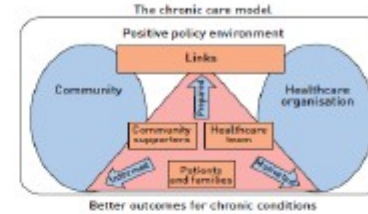
- ✓ Analisi di multi-database di grandi dimensioni relativi alla popolazione generale con individuazione di **nuovi fattori di rischio nell'insorgenza del diabete** (possibilità di predizione del 50% superiore) e individuazione della parte di **popolazione più a rischio** di svilupparlo
- ✓ Analisi di database clinici e amministrativi di pazienti diabetici **predizione dell'insorgenza delle complicanze**, analizzando e individuando i fattori e le variabili comportamentali e terapeutiche maggiormente correlate allo sviluppo di una specifica complicanza

Ambito della fenotipizzazione e della stratificazione del rischio

- ✓ Algoritmi di **fenotipizzazione** per individuare soggetti per lo screening e per la ricerca.
- ✓ Individuazione dei soggetti più a rischio
 - Uno studio su 65000 pazienti tipo 2 neodiagnosticati ha calcolato che il 10% dei soggetti assorbe il 68% delle risorse. Il compito dei metodi di analisi predittiva basati sui Big Data è proprio quello di individuare quel 10% dei soggetti più a rischio, su cui intensificare il trattamento, migliorando così gli esiti assistenziali con costi minori

Population health management: origini

1. Expanded Chronic Care Model (WHO): funzione integrativa delle cure primarie



2. Approccio di popolazione: focus sul rischio e prevenzione (life course approach)



3. «Messa a sistema» e sviluppo dei modelli della clinical governance:

a) PDTA

b) Dai percorsi alle reti (care networks)

c) Focus su presa in carico e aderenza (engagement)

d) Sviluppo dei sistemi informativi – BIG DATA e analytics

e) Revisione dei sistemi di finanziamento



1. Identificazione della popolazione e stratificazione del rischio: la predittività dello stato di salute

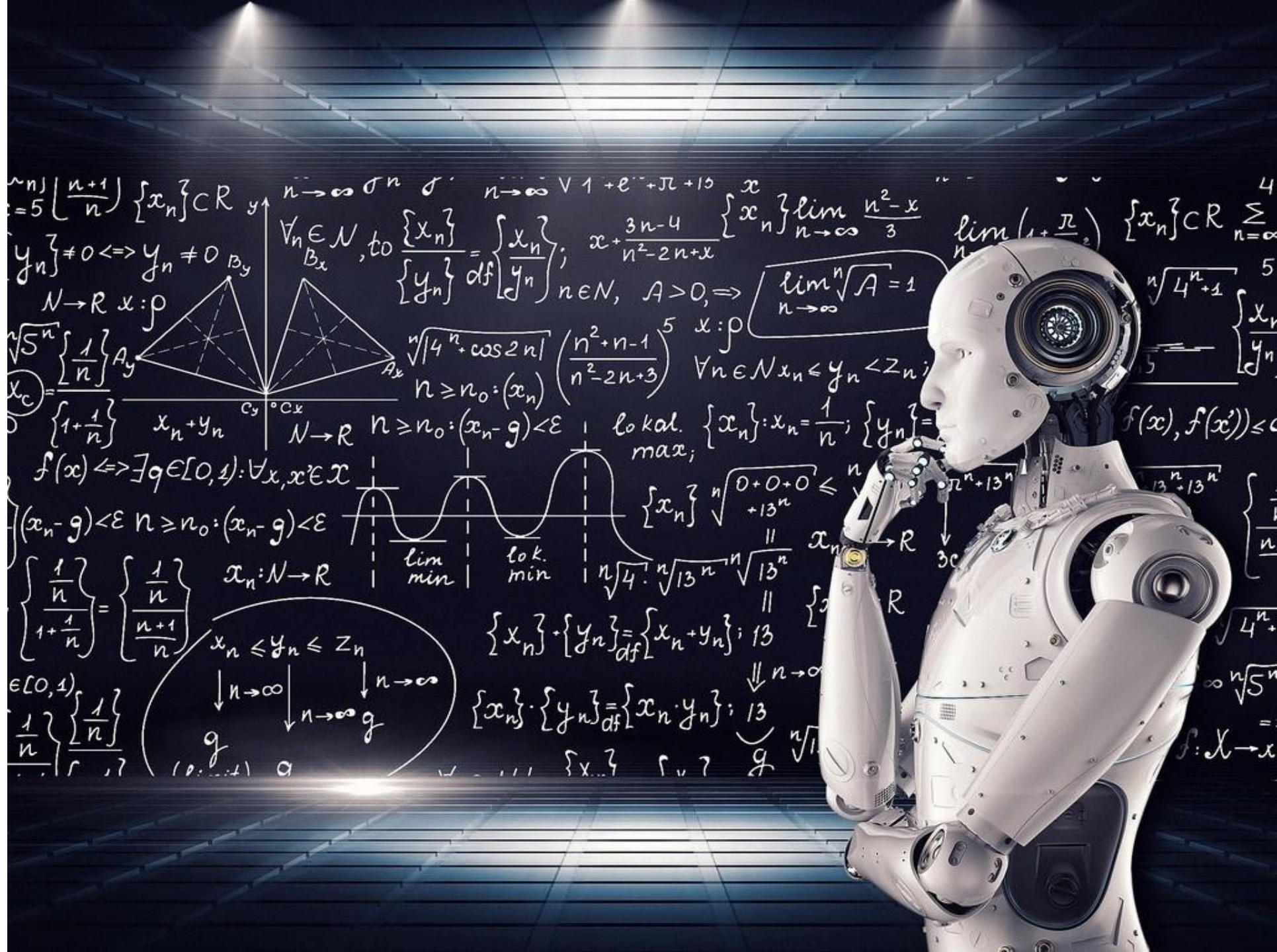
Nuova sfida è utilizzo dei BIG DATA, dei sistemi informativi e dei sistemi operativi per attivare modelli di stratificazione del rischio basati su:

- a) Stato di salute reale del pz (EHR)
- b) Utilizzo di più fonti
- c) Collaborazione con professionisti (data manager & care teams – data mining)

EHRs e strumenti informative (**automation**) nel PHM dovrebbero assolvere funzioni di:

- Identificazione popolazione
- Stratificazione
- Identificazione dei outliers (lower consumers)
- Engagement del pz
- Supporto al care management
- Misurazione outcome





Ambito della refertazione automatica

- ✓ **Diagnostica per immagini automatizzata** (indagini radiologiche, screening dermatologici, esame del fundus oculi)
- la classificazione automatizzata della RD presenta potenziali benefici quali l'aumento dell'efficienza, riproducibilità e copertura dei programmi di screening, riducendo gli ostacoli all'accesso e migliorando i risultati, fornendo diagnosi e trattamento precoci.



Carla Giordano, MD



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

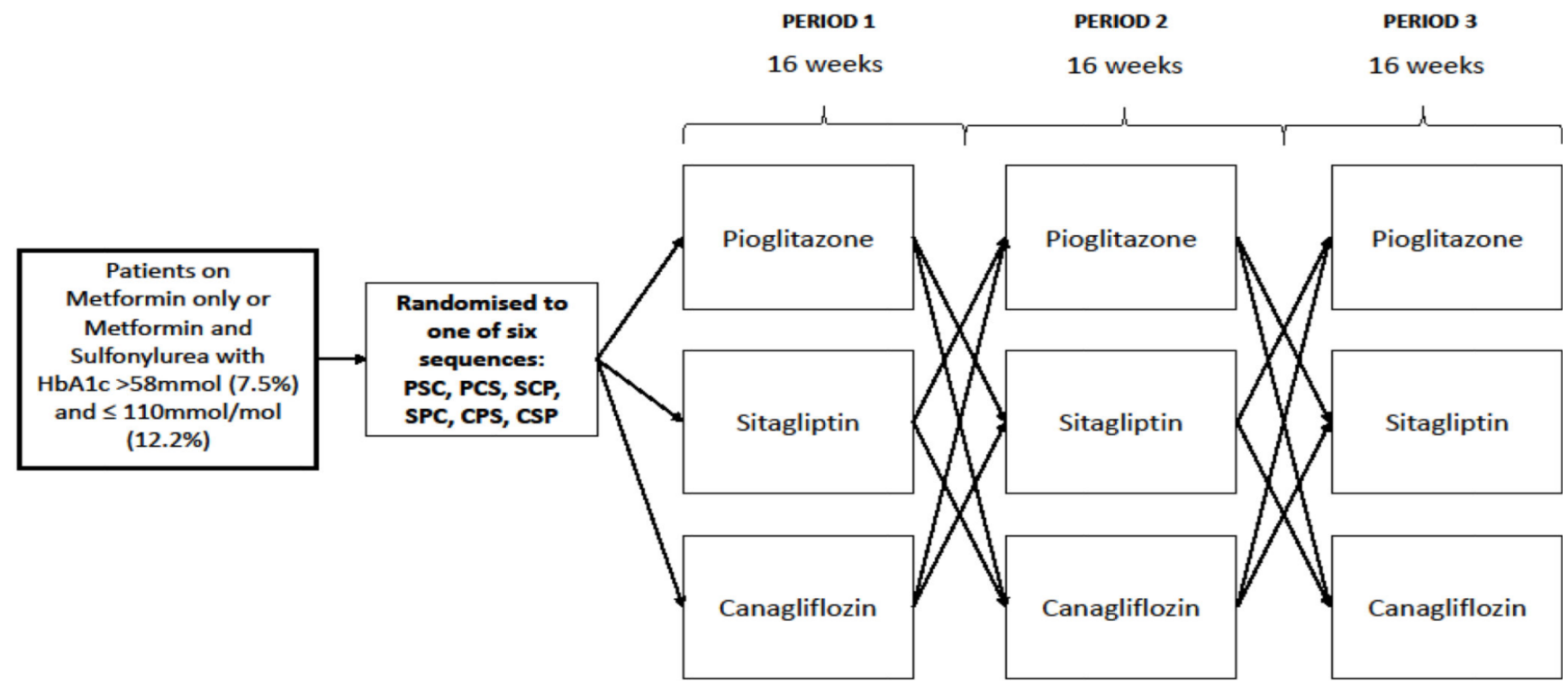


Figure 1. Study design for the TriMaster three-treatment, three-period crossover trial of pioglitazone, sitagliptin, and canagliflozin. Six sequences represent the 6 possible treatment orders for pioglitazone (P), canagliflozin (C) and sitagliptin (S). No washout between treatment periods.

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

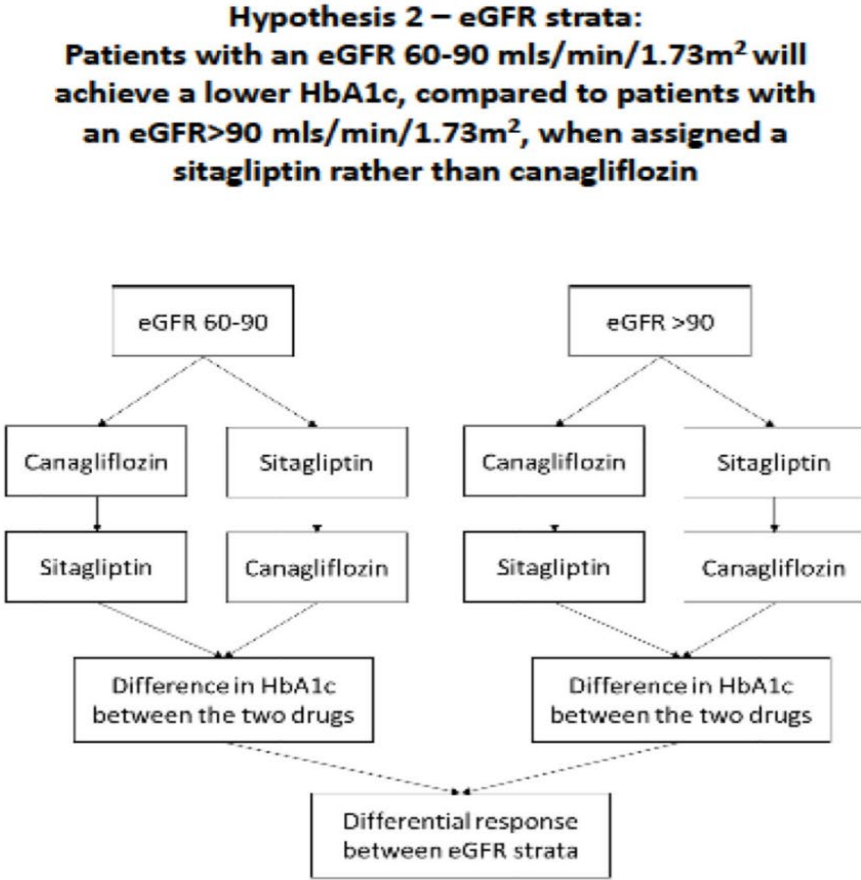
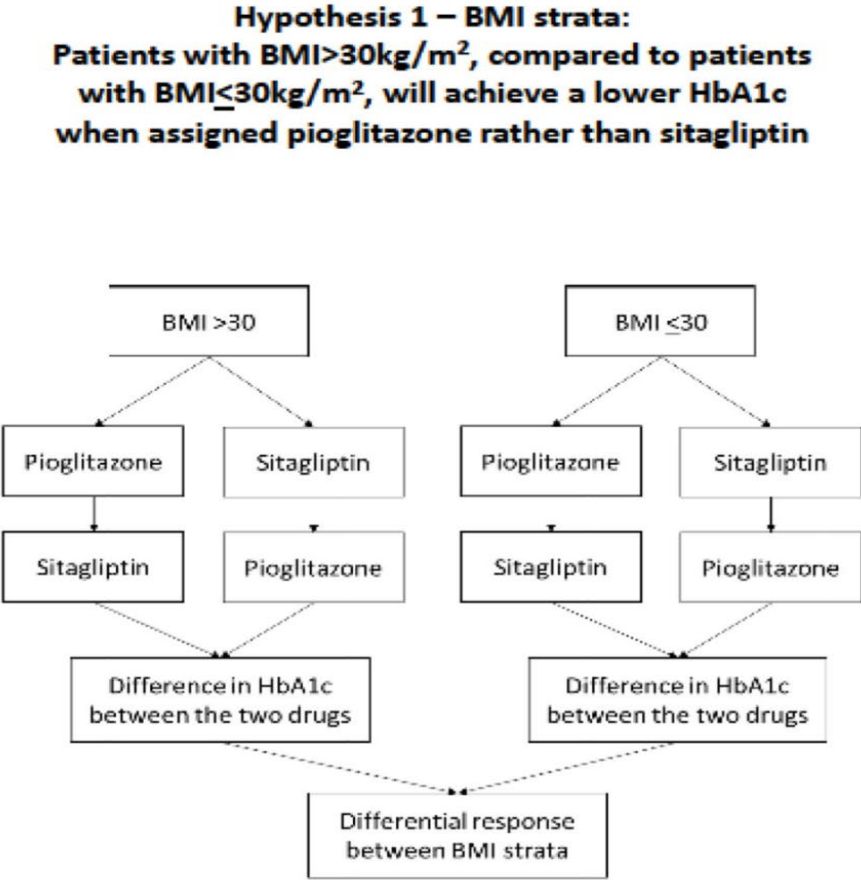


Figure 2. The two main hypotheses being tested in TriMaster

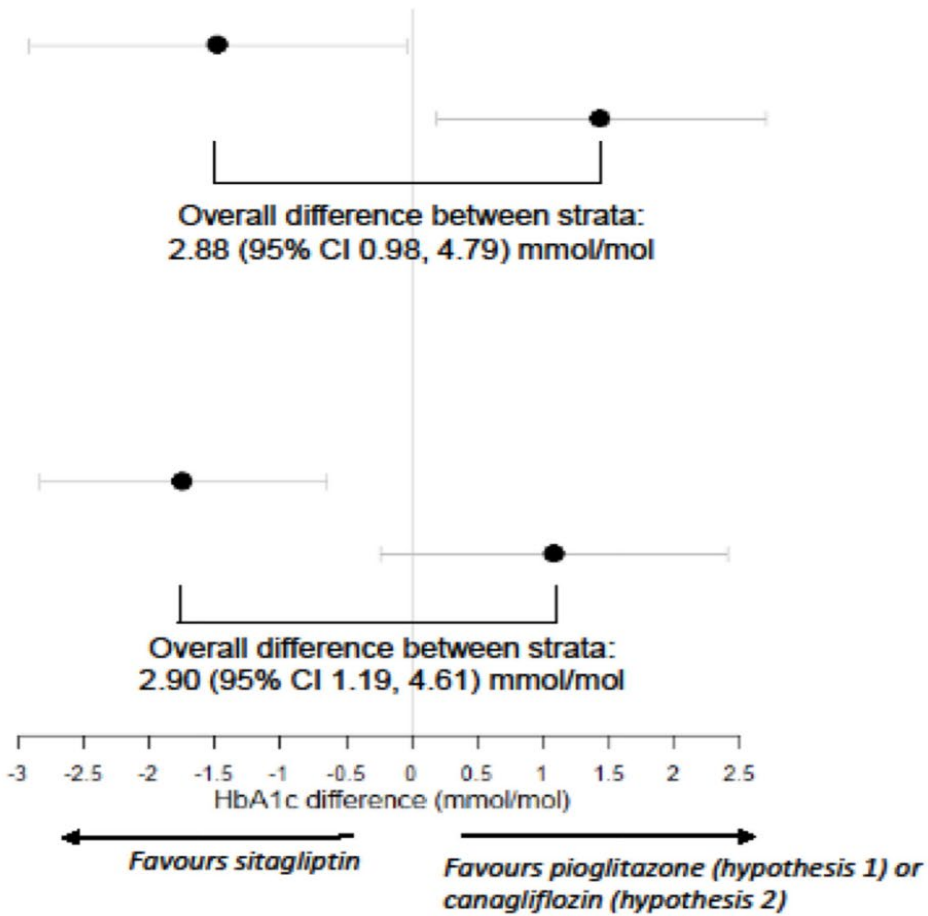
Patient stratification for determining optimal second and third line therapy for type 2 diabetes: the TriMaster study

a) Hypothesis 1 - Pioglitazone v Sitagliptin

Stratification by BMI

BMI≤30 (n=141)

BMI>30 (n=215)

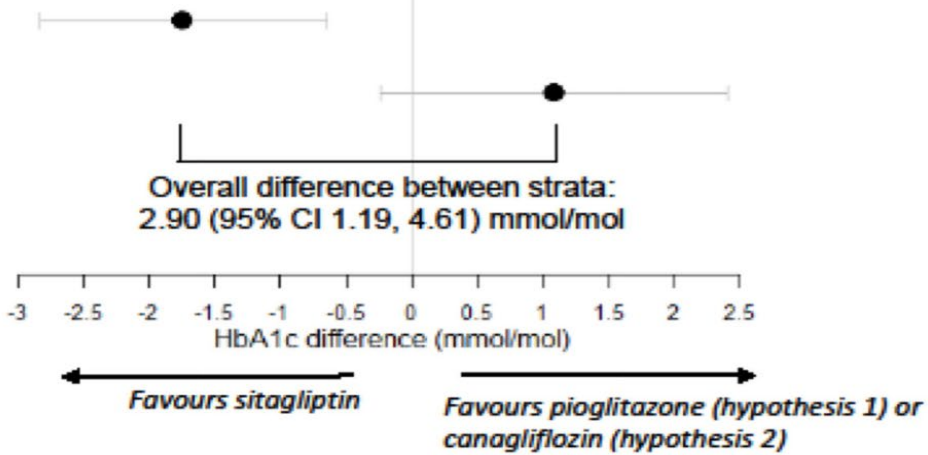


b) Hypothesis 2 - Canagliflozin v Sitagliptin

Stratification by renal function

eGFR 60-90 (n=163)

eGFR>90 (n=179)



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

Five components of the estimand for both study hypotheses

Target population	People with type 2 diabetes treated with metformin (+/- sulfon ylurea), with HbA1c >58mmol/mol (>7.5%) and <110mmol/mol (<12.2%) indicating treatment with another glucose-lowering therapy is needed.
Treatment condition of interest	Treatment with pioglitazone, sitagliptin, or canagliflozin
Variable of interest	On-treatment HbA1c
Comparative summary measure for results at population level	Difference in HbA1c when treated with the drug proposed best for a particular strata compared with the alternati ve drug in the other strata.
Handling of intercurrent events	In line with our primary endpoint def inition, participants who did not tak e therapy for sufficient time (discontinued before 12 weeks) or did not tak e sufficient quantities of therapy (<80% adherence on pill count) were e xcluded (see methods).

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

Primary analysis hypothesis 1. Absolute unadjusted values for HbA1c on pioglitazone and sitagliptin split by BMI strata and the corresponding mean difference between drugs, and between strata. P value assessed by a t test comparing the difference between drugs between strata.

BMI category	Drug	HbA1c (mmol/mol) Mean (SD)	Difference between drugs (mmol/mol) Mean (95% CI) *	Difference between strata (mmol/mol) (95% CI)	p
BMI<=30 n=141	Pioglitazone	59.7 (10.4)	1.48 (0.04, 2.91)	2.92 (0.99, 4.85)	0.003
	Sitagliptin	58.3 (8.6)			
BMI>30 n=215	Pioglitazone	59.0 (11.5)	-1.44 (-2.70, -0.19)		
	Sitagliptin	60.5 (11.2)			

* negative values favour pioglitazone.

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

Primary analysis hypothesis 2. Absolute unadjusted values for HbA1c on sitagliptin and canagliflozin split by eGFR strata and the corresponding mean difference between drugs, and between strata. P value assessed by a t test comparing the difference between drugs between strata.

eGFR category	Drug	HbA1c (mmol/mol) Mean (SD)	Difference between drugs (mmol/mol) Mean (95% CI) *	Difference between strata (mmol/mol) (95% CI)	p
eGFR60-90 (n=163)	Sitagliptin	59.0 (9.6)	-1.74 (-2.85, -0.65)	2.83 (1.09, 4.55)	0.002
	Canagliflozin	60.7 (8.7)			
eGFR>90 (n=179)	Sitagliptin	60.6 (11.7)	1.08 (-0.24, 2.41)		
	Canagliflozin	59.6 (9.4)			

* negative values favour sitagliptin

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

Extended Data Table 6

Weight difference by drug and strata. P value assessed by a t test comparing the difference
between drugs between strata.

		Weight (kg) Mean (SD)	Difference between drugs (mmol/mol) Mean (95% CI)*	Difference between strata (mmol/mol) (95% CI)*	p
BMI category					
BMI≤30 (n=186)	Pioglitazone	80.6 (10.6)	0.97 (0.61, 1.32)	0.93 (0.37, 1.48)	0.001
	Sitagliptin	79.6 (10.6)			
BMI>30 (n=265)	Pioglitazone	104.9 (16.4)	1.89 (1.50, 2.29)		
	Sitagliptin	103.0 (16.4)			
eGFR category					
eGFR 60-90 (n=213)	Sitagliptin	92.6 (16.9)	2.32 (1.95, 2.69)	0.13 (-0.40, 0.66)	0.6
	Canagliflozin	90.3 (16.9)			
eGFR>90 (n=241)	Sitagliptin	93.6 (20.1)	2.19 (1.81, 2.57)		
	Canagliflozin	91.3 (19.9)			

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Extended Data Table 7

Hypoglycaemia by hypothesised drug/strata combinations. Proportions experiencing hypoglycaemia for each of the hypothesised drug/strata combinations.

Hypothesis 1	Pioglitazone	Sitagliptin
BMI>30kg/m ²	33/263 (12.5%)	28/272 (10.3%)
BMI<=30kg/m ²	17/185 (9.2%)	16/182 (8.8%)
Hypothesis 2	Sitagliptin	Canagliflozin
eGFR 60-90	17/220 (7.7%)	12/221 (5.4%)
eGFR>90	27/234 (11.5%)	17/246 (6.9%)