SUMMIT

RHAPSODY
for precision therapy and prevention of diabetes

imidia
European combined excellence in diabetes research

BEAt DKD

DIRECT
DIABETES RESEARCH ON PATIENT STRATIFICATION

SOPHIA
Stratification of Obesity Phenotypes to Optimize Future Therapy

Maria F. Gomez
Lund University Diabetes Centre, Sweden

LUND UNIVERSITY DIABETES CENTRE

imi innovative medicines initiative

efpia

Reflections & learning lessons:

- *The power of public private partnerships in diabetes research*

- *Precision Medicine*

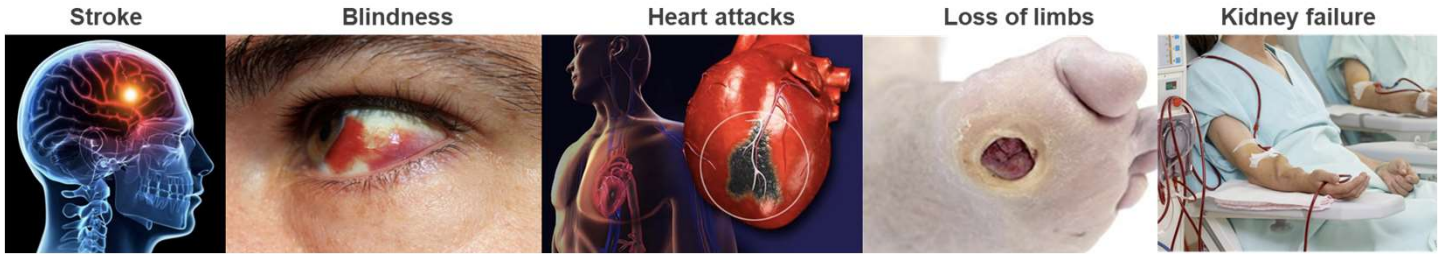
"The right prevention and treatment, to the right patients at the right time"

- *Preparedness to tackle health crises*

Maria F. Gomez
Lund University Diabetes Centre, Sweden

SUMMIT

SUrrogate markers for **M**icro- and **M**acro-vascular hard endpoints for **I**nnovative diabetes **T**ools



imidia
European combined excellence in diabetes research

2010-2015

- Genetic markers and soluble biomarkers
- Novel imaging techniques for monitoring progression in atherosclerosis and retinopathy
- Novel animal models for micro- and macrovascular complications to better replicate human disease
- Novel in silico methods for modelling and predicting diabetic complications

DIRECT
DIABETES RESEARCH ON PATIENT STRATIFICATION

2012-2019

2009-2015

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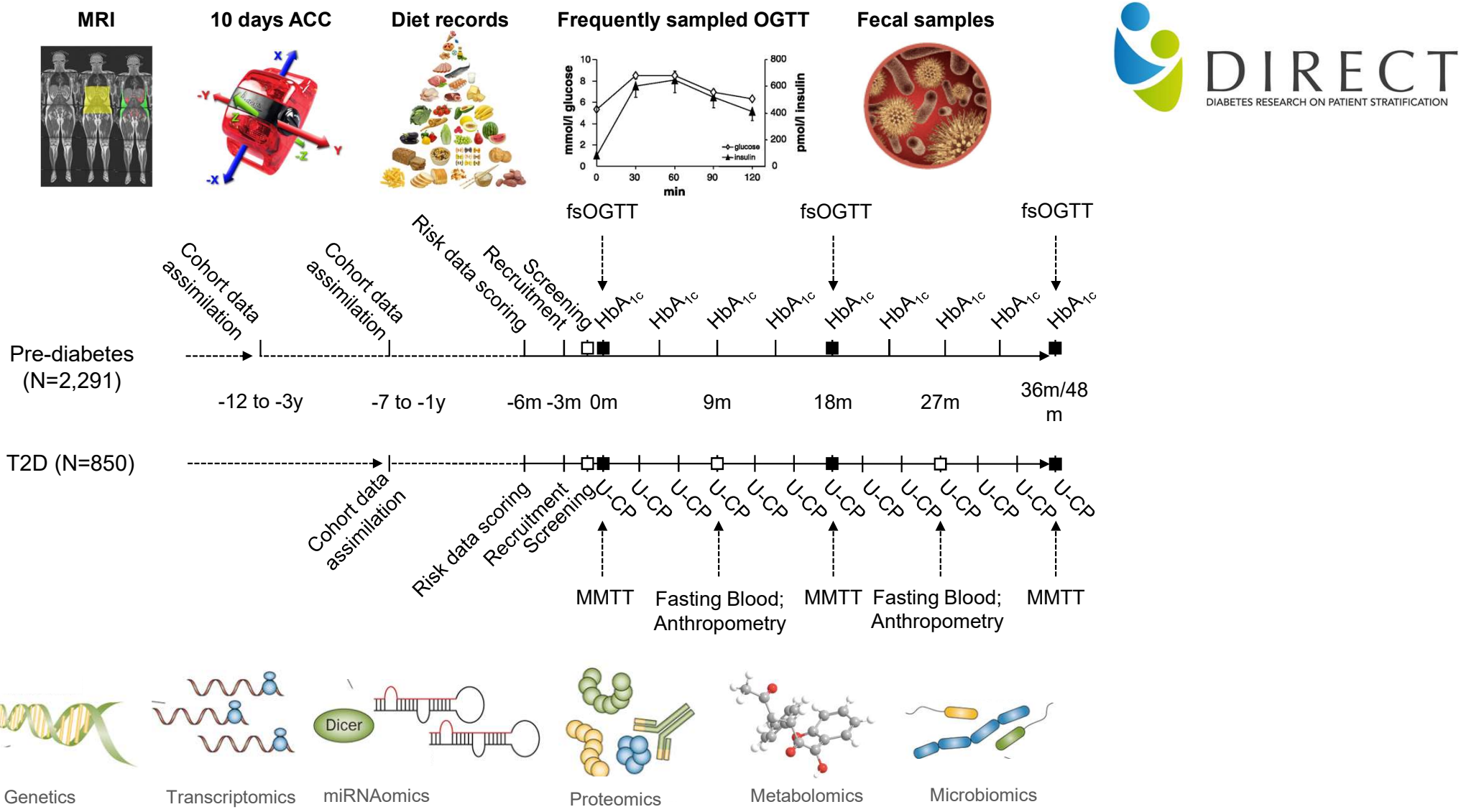

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The DIRECT Consortium. Koivula RW et al. *Diabetologia*, 2019

DIRECT
DIABETES RESEARCH ON PATIENT STRATIFICATION

Diabetologia
https://doi.org/10.1007/s00125-019-4906-1

ARTICLE

Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: descriptive characteristics of the epidemiological studies within the IMI DIRECT Consortium

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Abstract

Aims/hypothesis Here, we describe the characteristics of the In
Stratification (DIRECT) epidemiological cohorts at baseline an
Methods From a sampling frame of 24,682 adults of Europea
participants at varying risk of glycaemic deterioration were iden
circumference, use of antihypertensive medication, smoking s
prospective cohort study ($n = 2127$) (cohort 1, prediabetes ris
diabetes diagnosed 6–24 months previously ($n = 789$) into a se
took place at ~18 months (both cohorts) and at ~48 months (co
cohorts were studied in parallel using matched protocols across
Results Using ADA 2011 glycaemic categories, 33% ($n = 693$)
67% ($n = 1419$) had impaired glucose regulation. Seventy-six p
had the following characteristics (mean ± SD) at baseline: age
mmol/l; 2 h glucose 5.9 (1.6) mmol/l. At the final follow-up exa
fasting glucose 6.0 (0.6) mmol/l; 2 h OGTT glucose 6.5 (2.0)
lifestyle modification and 34% ($n = 272$) were treated with me
cent of participants in cohort 2 was male. Cohort 2 participants
BMI 30.5 (5.0) kg/m²; fasting glucose 7.2 (1.4) mmol/l; 2 h g

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-019-4906-1) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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Published online: 15 June 2019

PLOS MEDICINE

RESEARCH ARTICLE

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

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31 Department of Cell and Chemical Biology, Le
32 Molecular Epidemiology, Department of Bior

pmed.1003149 June 19, 2020

Article

A reference map of potential determinants for the human serum metabolome

https://doi.org/10.1038/s41586-020-2896-2
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Accepted: 29 September 2020
Published online: 11 November 2020
Check for updates

Noam Bar[1,5,6], Tal Korem[1,2,3,4,5,6], Omer Weissbrod[1,2,5], David Zeevi[1,5,7], Daphna Rothschild[1,2], Sigal Leviatan[1,2], Noa Kosower[1,2], Maya Lotan-Pompan[1,2], Adina Weinberger[1,2], Caroline I. Le Roy[8], Cristina Menni[8], Alessia Visconti[8], Mario Falchi[8], Tim D. Spector[8], The IMI DIRECT consortium*, Jerzy Adamski[9,10,11], Paul W. Franks[12,13], Oluf Pedersen[14] & Eran Segal[1,2,15]

The serum metabolome contains a plethora of biomarkers and causative agents of various diseases, some of which are endogenously produced and some that have been taken up from the environment[1]. The origins of specific compounds are known, including metabolites that are highly heritable[2,3], or those that are influenced by the gut microbiome[4], by lifestyle choices such as smoking[5], or by diet[6]. However, the key determinants of most metabolites are still poorly understood. Here we measured the levels of 1,251 metabolites in serum samples from a unique and deeply phenotyped healthy human cohort of 491 individuals. We applied machine-learning algorithms to predict metabolite levels in held-out individuals on the basis of host genetics, gut microbiome, clinical parameters, diet, lifestyle and anthropometric measurements, and obtained statistically significant predictions for more than 76% of the profiled metabolites. Diet and microbiome had the strongest predictive power, and each explained hundreds of metabolites—in some cases, explaining more than 50% of the observed variance. We further validated microbiome-related predictions by showing a high replication rate in two geographically independent cohorts[7,8] that were not available to us when we trained the algorithms. We used feature attribution analysis[9] to reveal specific dietary and bacterial interactions. We further demonstrate that some of these interactions might be causal, as some metabolites that we predicted to be positively associated with bread were found to increase after a randomized clinical trial of bread intervention. Overall, our results reveal potential determinants of more than 800 metabolites, paving the way towards a mechanistic understanding of alterations in metabolites under different conditions and to designing interventions for manipulating the levels of circulating metabolites.

We used mass spectrometry to profile serum samples from 491 healthy individuals for whom we had previously collected extensive clinical, lifestyle, dietary, genetics and gut microbiome data[10] (Methods, Extended Data Table 1). Our untargeted metabolomics analysis measured the levels of 1,251 metabolites, covering a wide range of biochemicals including lipids, amino acids, xenobiotics, carbohydrates, peptides and nucleotides, and approximately 30% unidentified compounds (Extended Data Fig. 1a, Methods, Supplementary Table 1). To classify unidentified metabolites and aid in biomarker discovery, we designed models that accurately predict the candidate biological pathway of the metabolites (Extended Data Fig. 2, Supplementary Note 1, Supplementary Table 2–5). Most metabolites we measured were prevalent across the cohort, including 498 metabolites that were detected in all samples and 1,104 metabolites that were detected in more than 50% of the samples (Extended Data Fig. 1b). After quality control (Methods), 475 individuals with high-quality data were included in the subsequent analyses.

To validate the accuracy of our metabolomic measurements, we compared the levels of creatinine and cholesterol to those obtained using standardized laboratory tests (Methods) that were performed independently on a second blood sample taken from the participants on the same visit, and found good agreement (creatinine, Pearson's $R = 0.87$; cholesterol, $R = 0.79$; Extended Data Fig. 1c, d). We further

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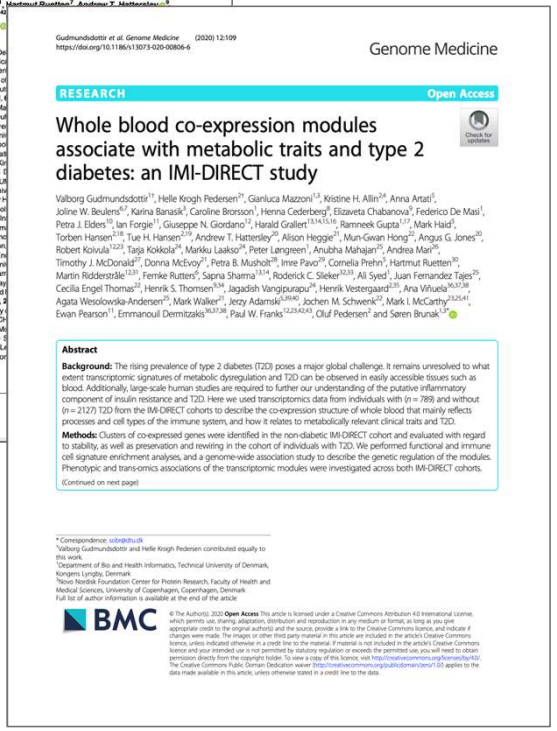

Gudmundsdottir et al. Genome Medicine (2020) 12:109
https://doi.org/10.1186/s13073-020-00806-6

Genome Medicine

RESEARCH Open Access

Whole blood co-expression modules associate with metabolic traits and type 2 diabetes: an IMI-DIRECT study

Valborg Gudmundsdottir[1†], Helle Krogh Pedersen[2†], Gianluca Mazzoni[1,3], Kristine H. Allin[2,4], Anna Artati[5], Joline W. Beulens[6,7], Karina Banasik[2], Caroline Brorsson[1], Henna Cederberg[8], Elizaveta Chabanova[9], Federico De Masi[1], Petra J. Elders[10], Ian Forgie[11], Giuseppe N. Giordano[12], Harald Grallert[13,14,15,16], Ramneek Gupta[1,17], Mark Haid[5], Torben Hansen[2,18], Tue H. Hansen[2,19], Andrew T. Hattersley[20], Alison Heggie[21], Mun-Gwan Hong[22], Angus G. Jones[20], Robert Koivula[12,23], Tarja Kokkola[24], Markku Laakso[24], Peter Løngreen[1], Anubha Mahajan[25], Andrea Mari[26], Timothy J. McDonald[27], Donna McEvoy[21], Petra B. Musholt[28], Imre Pavo[29], Cornelia Prehn[5], Hartmut Ruetten[30], Martin Ridderstråle[12,31], Fernke Rutters[6], Sapna Sharma[13,14], Roderick C. Slieker[32,33], Ali Syed[1], Juan Fernandez Tajes[25], Cecilia Engel Thomas[22], Henrik S. Thomsen[9,34], Jagadish Vangipurapu[24], Henrik Vestergaard[2,35], Ana Viñuela[36,37,38], Agata Wesolowska-Andersen[35], Mark Walker[21], Jerzy Adamski[5,39,40], Jochen M. Schwenk[22], Mark I. McCarthy[23,25,41], Ewan Pearson[11], Emmanouil Dermitzakis[36,37,38], Paul W. Franks[12,23,42,43], Oluf Pedersen[2] and Søren Brunak[1,3*]

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†Valborg Gudmundsdottir and Helle Krogh Pedersen contributed equally to this work.
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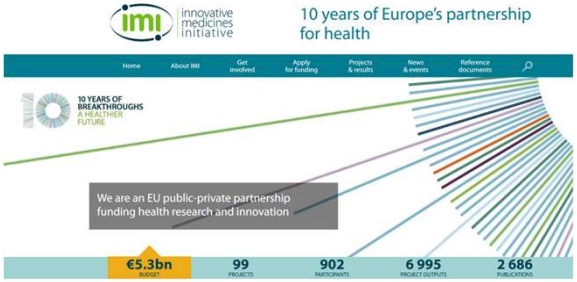
Abstract

Background: The rising prevalence of type 2 diabetes (T2D) poses a major global challenge. It remains unresolved to what extent transcriptomic signatures of metabolic dysregulation and T2D can be observed in easily accessible tissues such as blood. Additionally, large-scale human studies are required to further our understanding of the putative inflammatory component of insulin resistance and T2D. Here we used transcriptomics data from individuals with ($n = 789$) and without ($n = 2127$) T2D from the IMI-DIRECT cohorts to describe the co-expression structure of whole blood that mainly reflects processes and cell types of the immune system, and how it relates to metabolically relevant clinical traits and T2D.

Methods: Clusters of co-expressed genes were identified in the non-diabetic IMI-DIRECT cohort and evaluated with regard to stability, as well as preservation and rewiring in the cohort of individuals with T2D. We performed functional and immune cell signature enrichment analyses, and a genome-wide association study to describe the genetic regulation of the modules. Phenotypic and trans-omics associations of the transcriptomic modules were investigated across both IMI-DIRECT cohorts.

(Continued on next page)



"the citation impact of IMI papers is twice the world average and significantly higher than the EU average"

SUMMIT

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DIABETES RESEARCH ON PATIENT STRATIFICATION

SOPHIA
Stratification of Obesity Phenotypes to Optimize Future Therapy

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imi innovative medicines initiative

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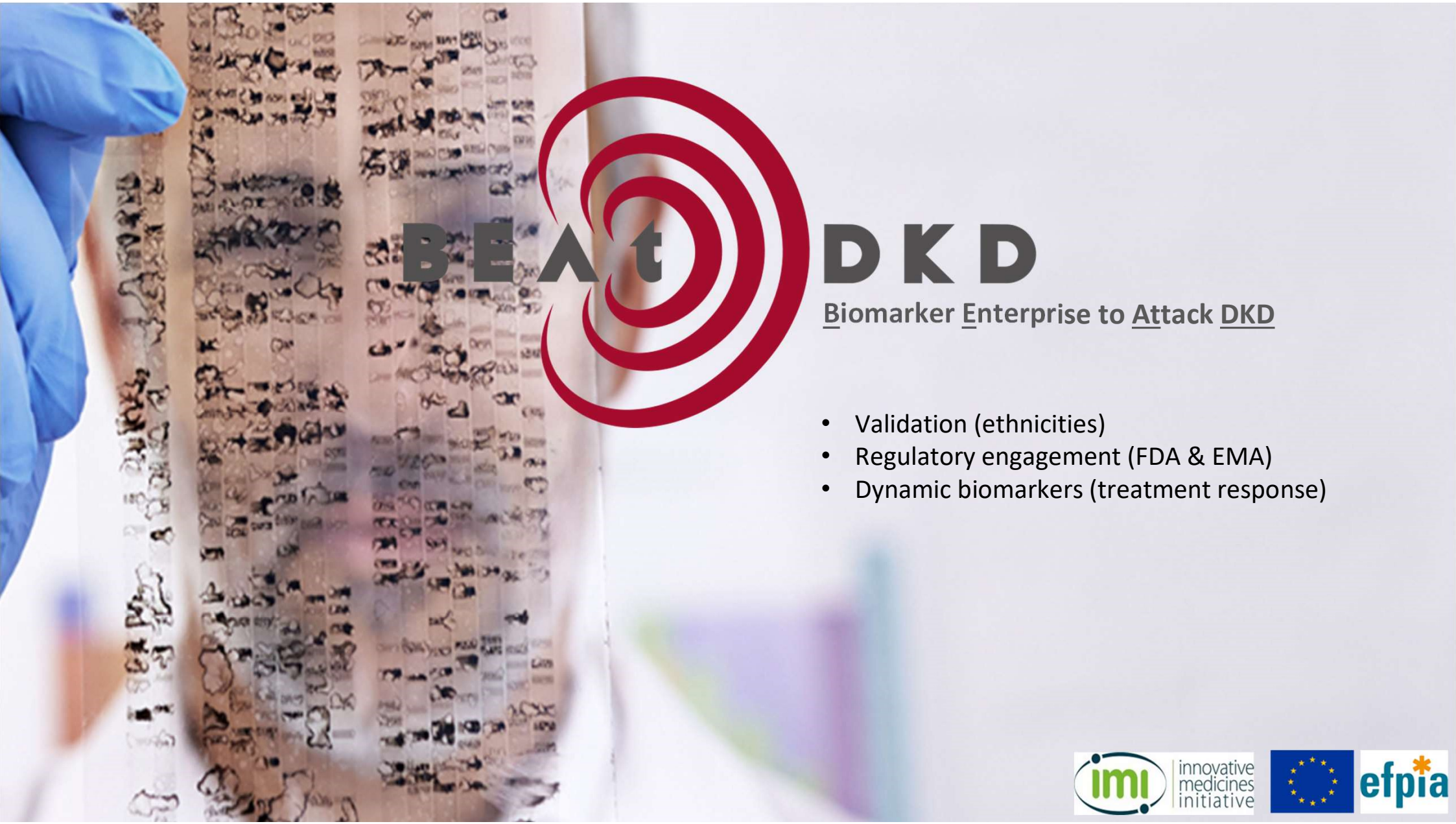


BEAt DKD

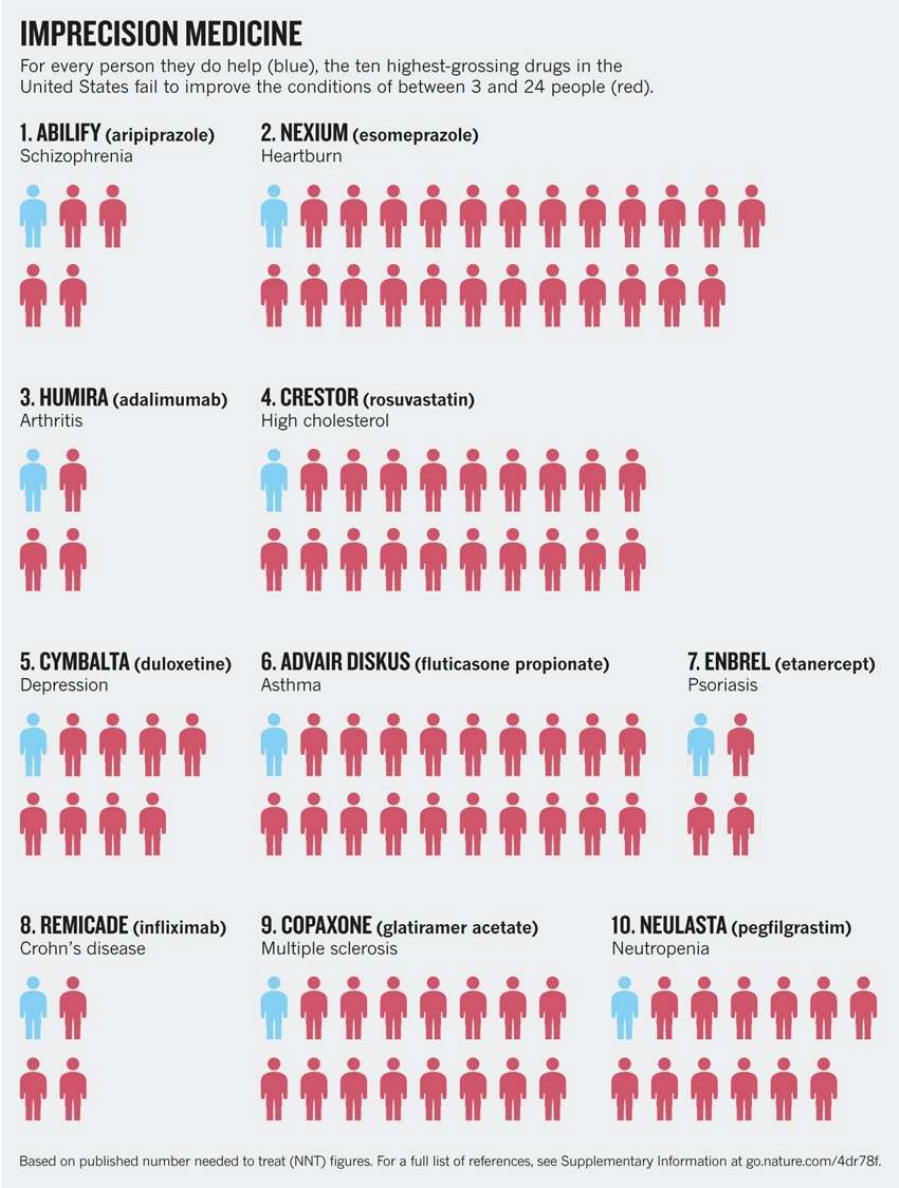
Biomarker Enterprise to Attack DKD

- Validation (ethnicities)
- Regulatory engagement (FDA & EMA)
- Dynamic biomarkers (treatment response)

imi innovative medicines initiative

efpia

Maximizing synergies between existing consortia, academia & industry for effective utilization of available resources – Data Federation for sensitive data



Schork NJ. *Nature*. 2015;520(7549):609-11

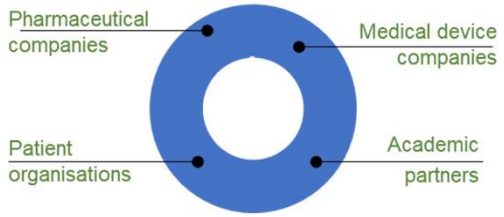
- ACE inhibitors (ACEi) in 1993
- Angiotensin-Receptor Blockers (ARBs) in 2001

= slow progression of renal disease in T2D patients by ~20% compared to the "standard" glucose lowering and blood pressure lowering therapies, but residual renal and cardiovascular risk remained extremely high

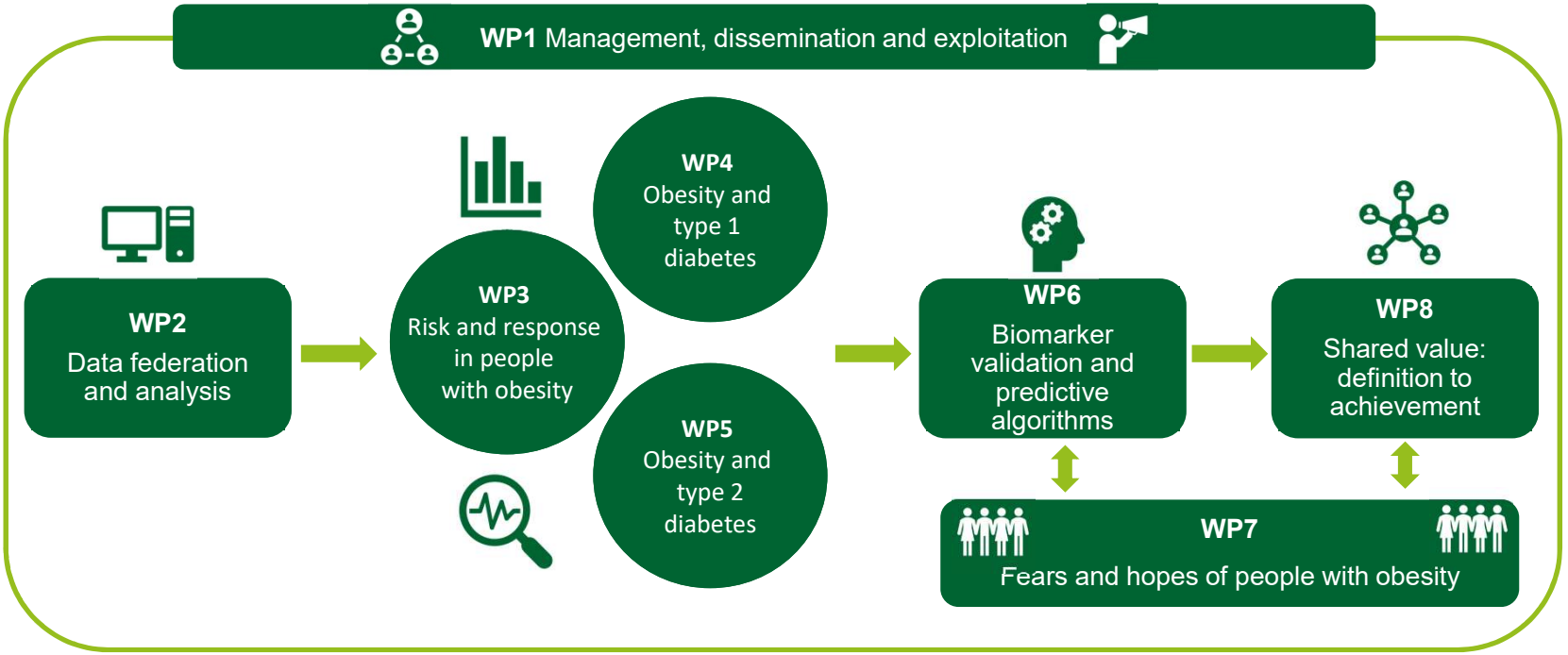
- endothelin receptor antagonist (ERa) atrasentan
- sodium glucose cotransporter 2 (SGLT2)
- aldosterone inhibitors (FINERENONE, EPLERENONE)
- statins

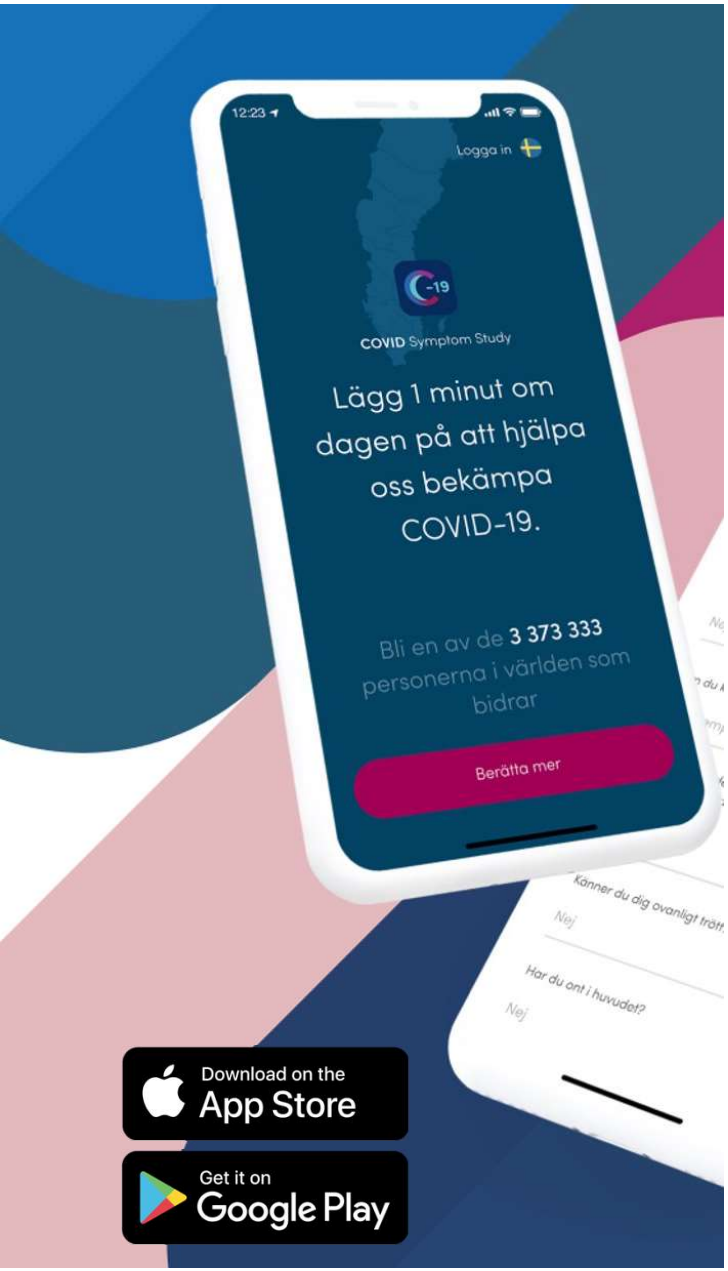
= not all patients benefit from the treatments – abandon the idea of "one size fits all"

SOPHIA
Stratification of Obesity Phenotypes to Optimize Future Therapy



SOPHIA Work Package (WP) overview





COVID Symptom Study

- **~4,6 million participants** in 3 countries (UK, USA, Sweden)
- **~370 million data entries** obtained through a mobile device app documenting symptoms, risk factors, use of PPE, behaviors, test results, vaccinations
- Weekly reports produced and sent to leaders of regional and national public health authorities
- A dashboard showing infection trends on a regional and national level is maintained (https://csss-resultat.shinyapps.io/csss_dashboard/)
- High-profile publications (Drew et al *Science* 2020; Menni et al *Nature Medicine* 2020; Varvasky et al *Lancet Public Health*. 2020; Lee et al *Oncologist*. 2021; Nguyen et al *Lancet Public Health*. 2020; Sudre et al *Science Advances*. 2020; Sudre et al *Nature Medicine* 2021)
- Webpage UK https://covid.joinzoe.com/
- Webpage Sweden https://www.covid19app.lu.se/

ZOE & KING'S College LONDON

LUNDS UNIVERSITET

UPPSALA UNIVERSITET

Clinical characteristics and genetics of novel subtypes of adult onset diabetes

Emma Ahlqvist, MSc, PhD

Associate Professor,

Lund University Diabetes Centre, Malmö, Sweden

Heterogeneity of diabetes

Diabetes is defined by high glucose but causes for hyperglycemia differ
Type 2 diabetes is a diagnosis of exclusion

Autoimmune:
Type 1 diabetes (T1D)
Latent Autoimmune Diabetes in Adults (LADA)

Genetic:
Maturity Onset Diabetes in Young (MODY)
Neonatal diabetes

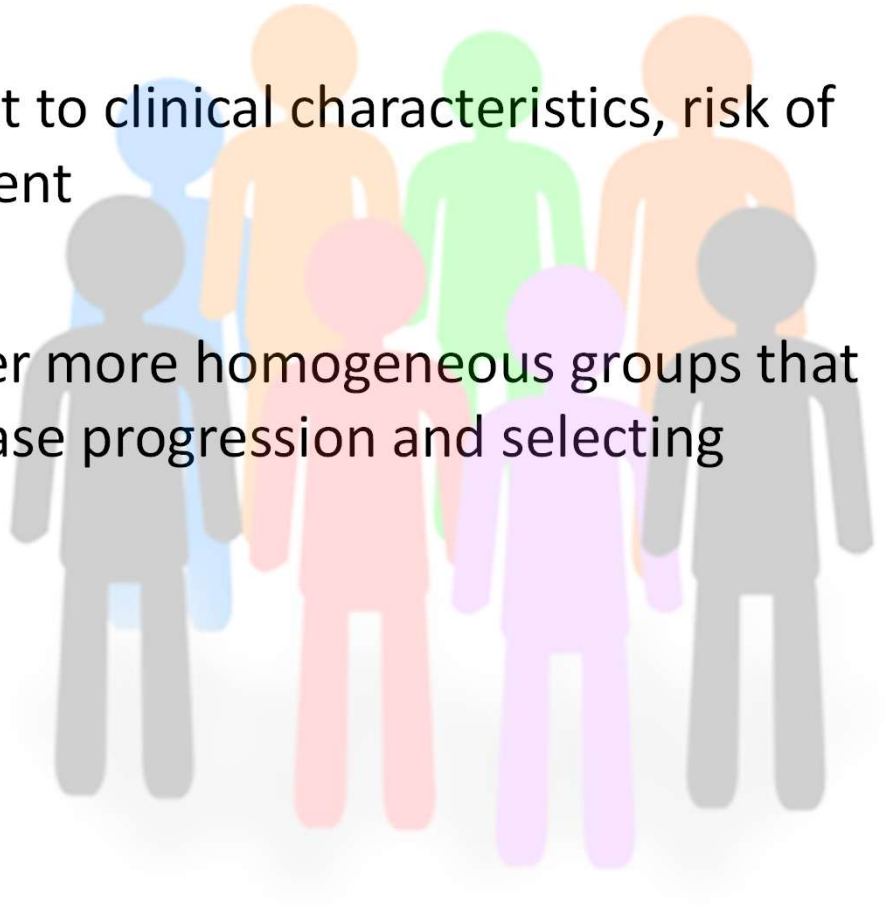
Secondary diabetes
.
.

Type 2 diabetes (T2D)

Heterogeneity in T2D

- Individuals with T2D differ with respect to clinical characteristics, risk of complications and response to treatment

- Can we divide T2D patients into smaller more homogeneous groups that are clinically useful for predicting disease progression and selecting therapy?



Ahlqvist et al. Lancet Diabetes & Endocrinology, 2018

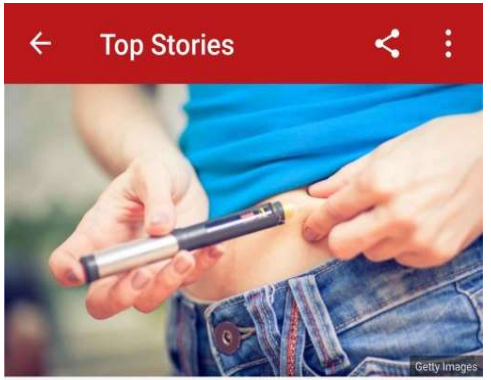
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*

Summary

Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.

Lancet Diabetes Endocrinol 2018
Published Online
March 1, 2018



Could there be five types of diabetes rather than just two?

Diabetes is actually five separate diseases, research suggests

By James Gallagher
Health and science correspondent, BBC News
6 hours ago | Health

Cluster analysis

- Cluster analysis is a method for data driven grouping of individuals by similarity

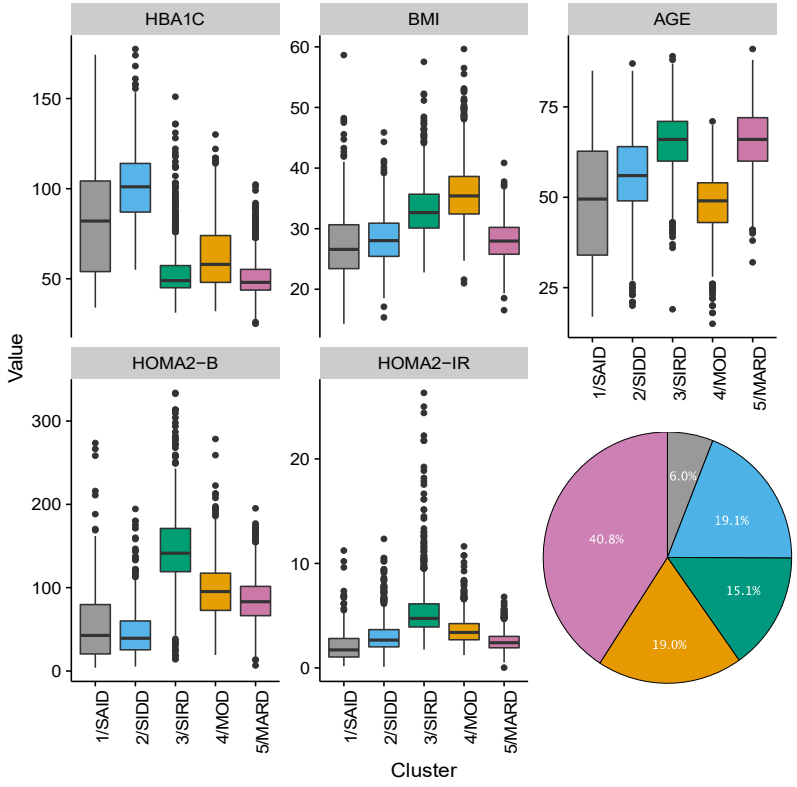
- Cohorts
  - ANDIS (All New Diabetics in Scania) (N=8980)
    - New onset diabetes of all types
    - Children and monogenic/secondary diabetes were excluded

- Cluster variables
  - Presence of GAD65 antibodies
  - HbA1c at diagnosis
  - BMI
  - Age at diagnosis
  - C-peptide based HOMA2-B (insulin secretion)
  - C-peptide based HOMA2-IR (insulin resistance)

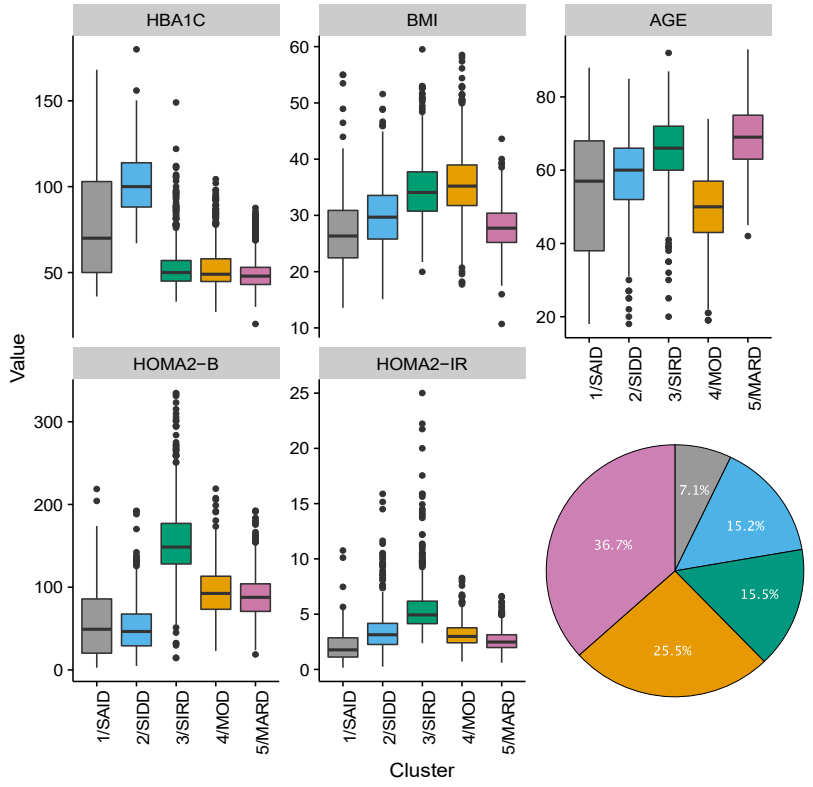
Ahlqvist et al, Lancet Diabetes and Endocrinology, 2018

Clustering results in ANDIS

Men n=5.334



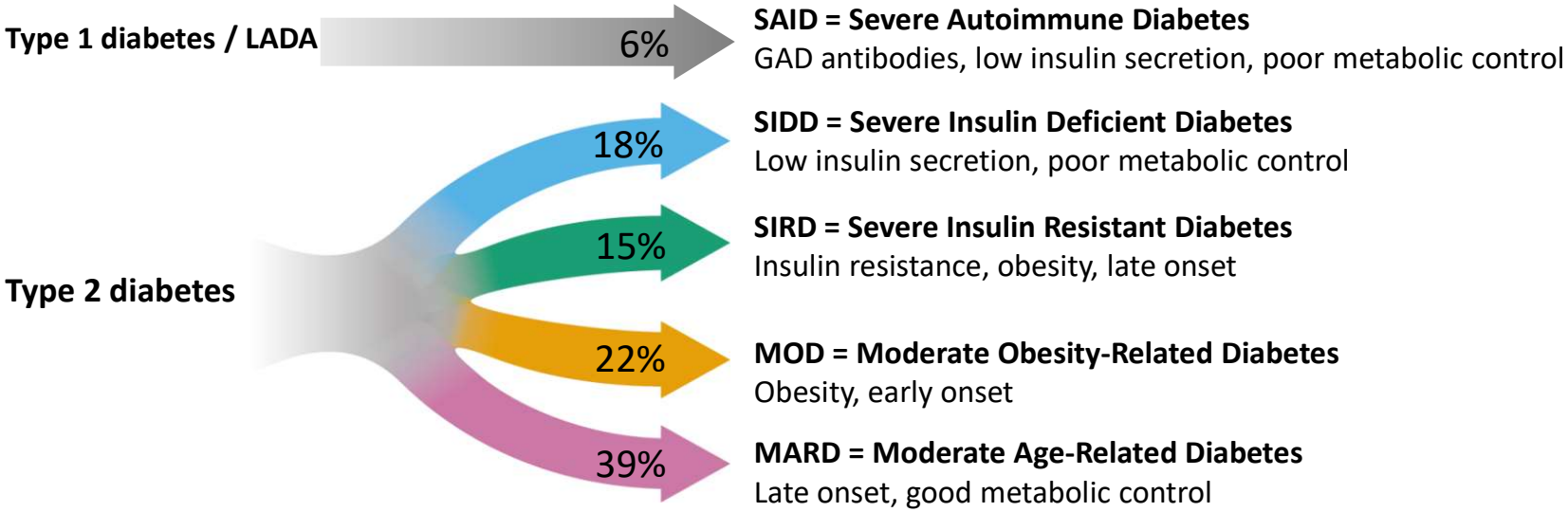
Women n=3.646



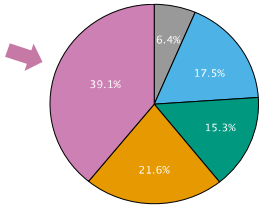
Ahlqvist et al, Lancet Diabetes and Endocrinology, 2018

Summary clusters

We can reproducibly divide patients into five subgroups with different characteristics and progression



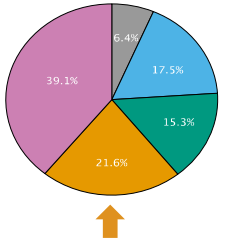
This clustering approach has been replicated in numerous cohorts



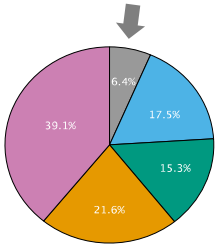
MARD - Moderate age-related diabetes

- 39% of patients
- Relatively old at diagnosis (mean age 67 years)
- Moderately over weight (mean BMI = 28)
- Relatively low blood glucose
- Relatively low risk of complications

MOD – Moderate Obesity-related Diabetes



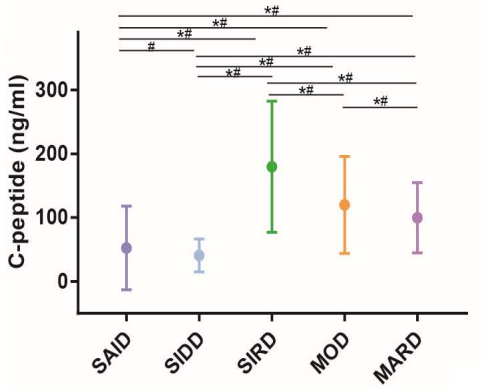
- 22% of patients
- Obese (mean BMI = 36)
- Early onset (mean age at diagnosis = 49 years)
- Relatively low blood glucose levels
- Relatively low risk of complications
- BUT early onset means a long time for complications to develop

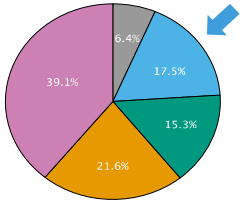


SAID - Severe autoimmune diabetes

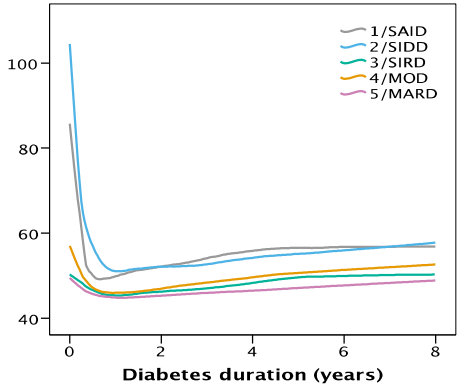
- 6% of patients (>18 years old)
- Autoantibody positive (GADA) = includes T1D and LADA
- Poor insulin secretion
- Relatively early onset of diabetes (mean ~50 years)
- High glucose levels(HbA1c) = poor metabolic control

Insulin secretion





Blood glucose (HbA1c) over time

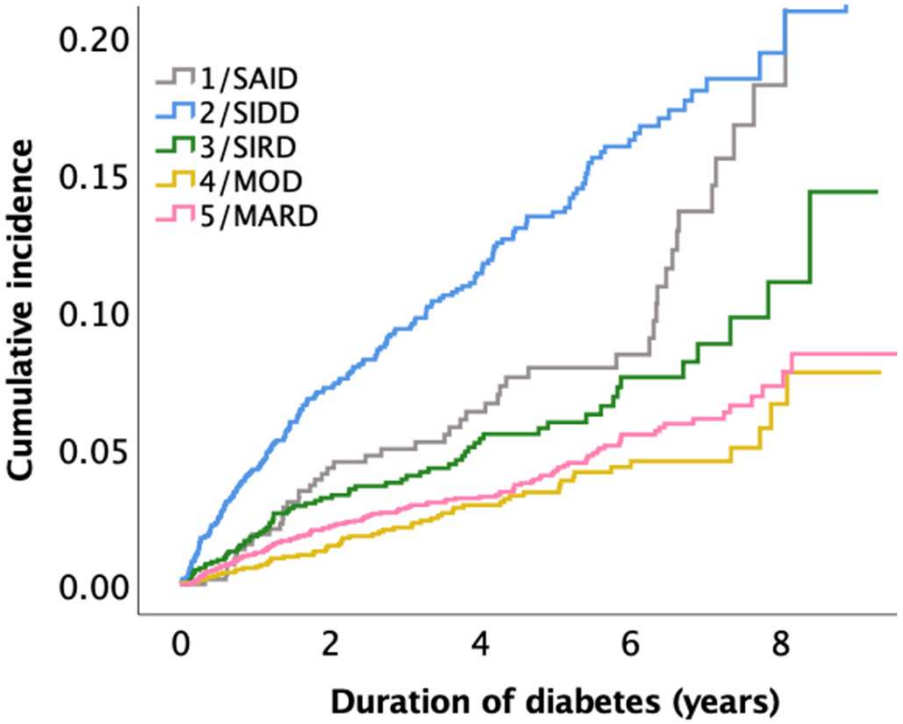


SIDD - Severe insulin-deficient diabetes

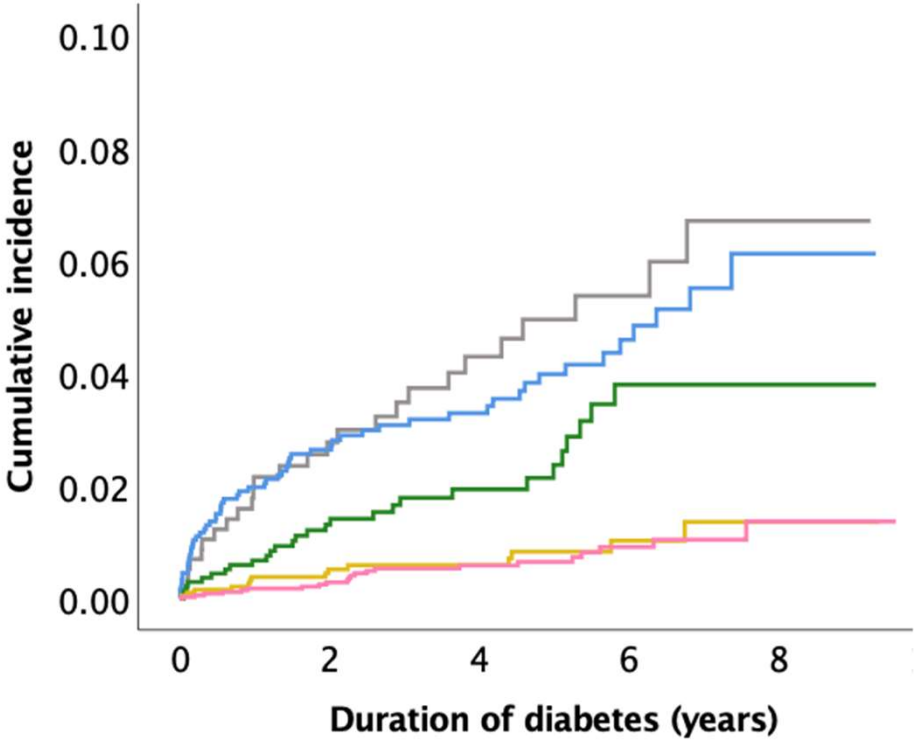
- 18% of patients
- Poor insulin secretion
- Poor metabolic control
- Overweight (mean BMI = 29)
- Relatively early onset (mean age at diagnosis = 57 years)
- More difficult to treat

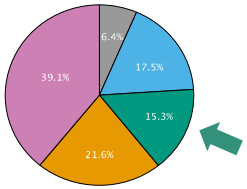
Diabetic complications

Retinopathy



Neuropathy



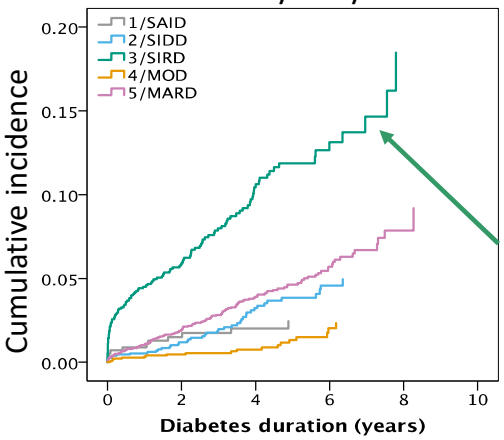


SIRD - Severe insulin-resistant diabetes

- 15% of patients
- Severe insulin resistance and obesity (mean BMI = 34)
- Late onset (mean age at diagnosis = 65 years)
- Approximately the same glucose leves as mild diabetes forms, MARD and MOD
- Approximately the same treatment
- Much higher risk of kidney complications and fatty liver disease

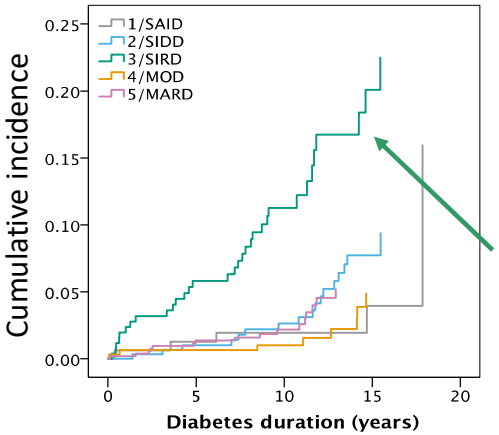
ANDIS

eGFR<45 mL/min/1·73m^2



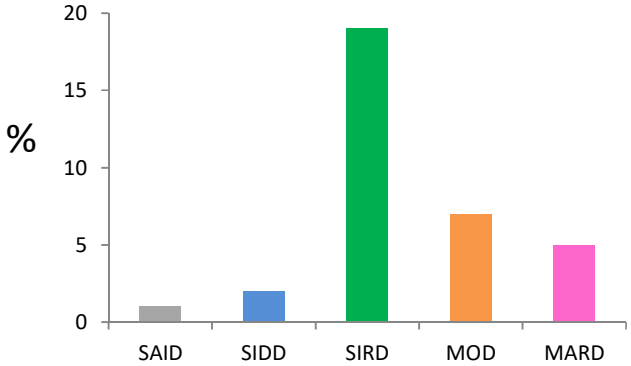
SDR

ESRD eGFR<15 mL/min/1·73m^2



German Diabetes Study

Hepatocellular lipid content

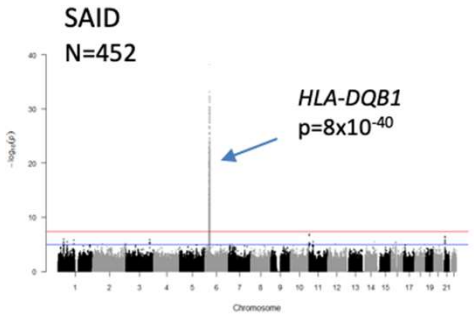


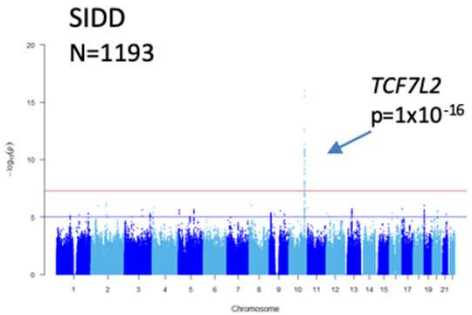
Adapted from

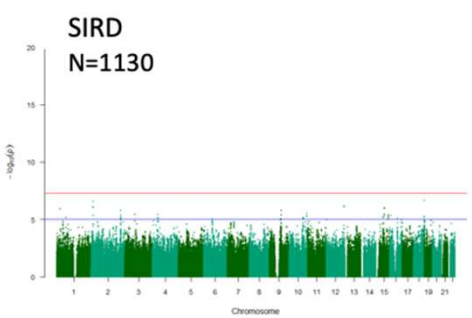
Zaharia et al, Lancet Diabetes and Endocrinology, 2019

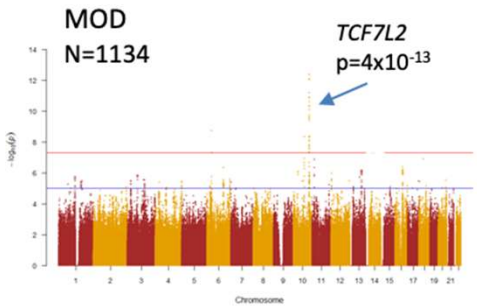
Genome-Wide Association Study (GWAS)

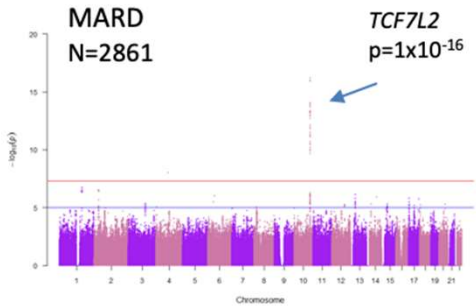
Compared with diabetes free individuals N=2744











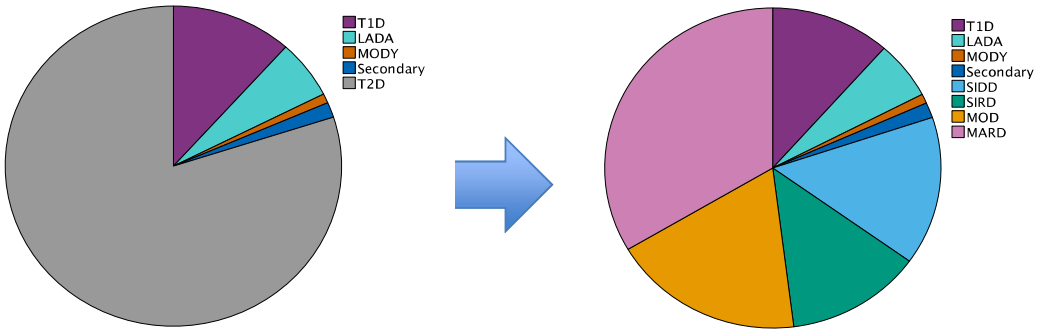
Risk variants are differentially associated with subtypes

Risk score	SAID	SIDD	SIRD	MOD	MARD
BMI	17%	12%	22%	29%	4%
Insulin secretion	1%	33%	5%	29%	31%
Insulin sensitivity	8%	17%	16%	15%	15%

Mansour Aly et al, MedRxiv, 2020

Summary

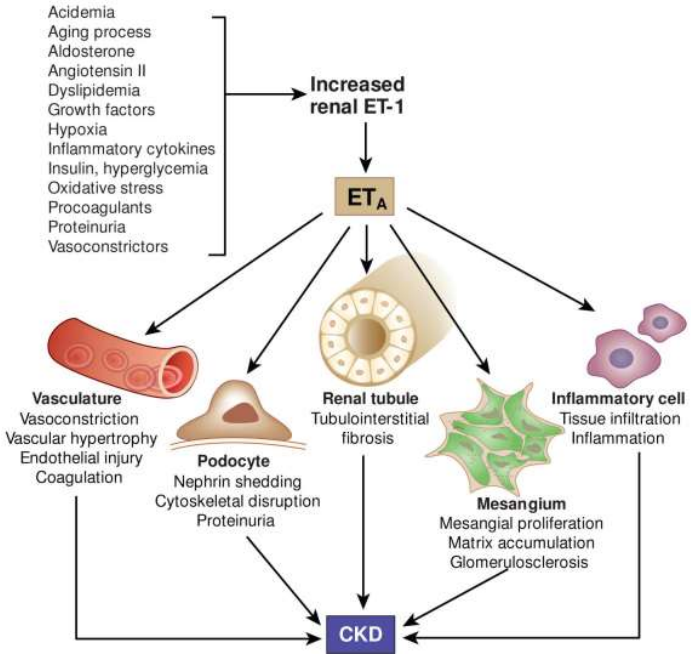
- Three severe forms of diabetes
  - Autoimmune (SAID)
  - Insulin deficient (SIDD)
  - Insulin resistant (SIRD)
- Two moderate forms of diabetes
  - Obesity-related (MOD)
  - Age-related (MARD)



- SIDD has the highest risk of diabetic retinopathy and neuropathy
- SIRD has the highest risk of diabetic kidney disease and NAFLD
- Important not to focus only on HbA1c to evaluate disease progression and response to therapy
- SIDD and SIRD patients develop complications very early and would benefit from early identification and treatment
- Genetics suggest differences in pathogenesis

Extra slides

Targeting Vascular Stress in CKD: Endothelin Signaling Pathway

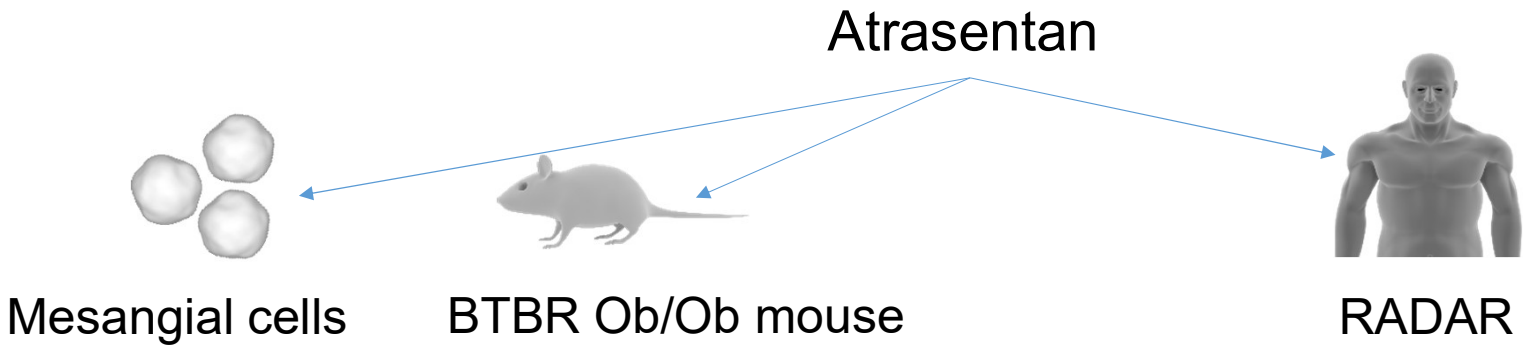


from Kidney Int 2014 86(5): 896-904

- Endothelin 1 (ET1, EDN1) is increased by range of factors present in proteinuric glomerular diseases
- EDN1 is mainly produced by endothelial cells
- Targets vascular smooth muscle, mesangial, inflammatory and epithelial cells
- Endothelin Receptor blockade successfully developed for DKD and glomerular diseases

Identification of molecular pathways & biomarkers associated with response to atrasentan

H L Heerspink



W. Ju, P. Perco, V. Nair, S. Belur, F. Burdet, A. Thorenz, A. Kannt, M. Gomez, C Alpers, M. Kretzler, H L Heerspink on behalf of the BEAt-DKD consortium.

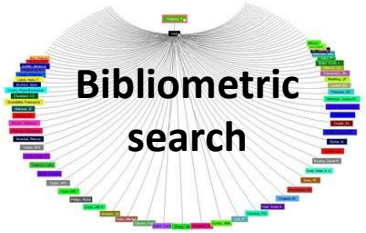
GENERAL APPROACH FOR BM DISCOVERY IN BEAt-DKD

Table 2. Clinical trials

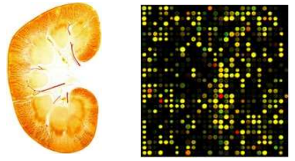
Study	Drug	Drug class	N patients
NEPHRON-D	Lisinopril / Losartan	ACEI/ARB	1448
ONTARGET[3]	Ramipril / Telmisartan	ACEi/ARB	6972
VARIETY[4]	Benazepril/Valsartan	ACE/ARB	613
VALID[4]	Benazepril/Valsartan	ACE/ARB	103
IRMA-2	Irbesartan	ARB	165
SPIRIL	Spironolactone	MRA	116
PRIORITY[5]	Spironolactone	MRA	670
PLANET I	Atorvastatin/Rosuvastatin	Statin	325
SUN-macro	Sulodexide	Glycosaminoglycan	1167
RADAR	Atrasentan	ERA	211
SONAR[3,6]	Atrasentan	ERA	4000
ACCORD-BP	Intensive BP, HbA1c lowering and lipid trial	BP targets, Hba1c target, Fenofibrate	10251
IMPROVE	Dapagliflozin	SGLT2	36
Lilly GFRF[9]	TGFb1 monoclonal Ab	Novel target	315
DIABASI[4]	Acetyl-L-carnitine	Antioxidant	229
CRESO[4]	Diet		74
CRESO 2[4]	Diet		66
PROCEED[4]	Paricalcitol	VDR agonist	115
Iron-deficient NDD-CKD patients	Iron isomaltoside	Iron isomaltoside	351

- ACEi / ARB combinations
  (VALID / NEPHRON-D / ONTARGET)
- Statins (PLANET 1 and PLANET 2)
- Endothelin Receptor Antagonists
  (RADAR / SONAR)
- Sodium Glucose Co-transport inhibitors
  (IMPROVE – DAPKID / RED-D)

1: Literature search to assess effects of drug of interest on molecular markers

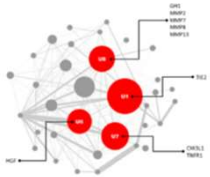


2: Transcriptomic profiling of a drug's molecular effect in cells, tissues and human blood/urine samples



3: Bioinformatics to retrieve a drug effect signature

4: Mapping drug (SOC) MoA model with established diabetic nephropathy model



5: Creating a short-list of biomarkers involved in DN and targeted by the drug of interest