Precision Medicine in Diabetes Mellitus: Where Are We Now?

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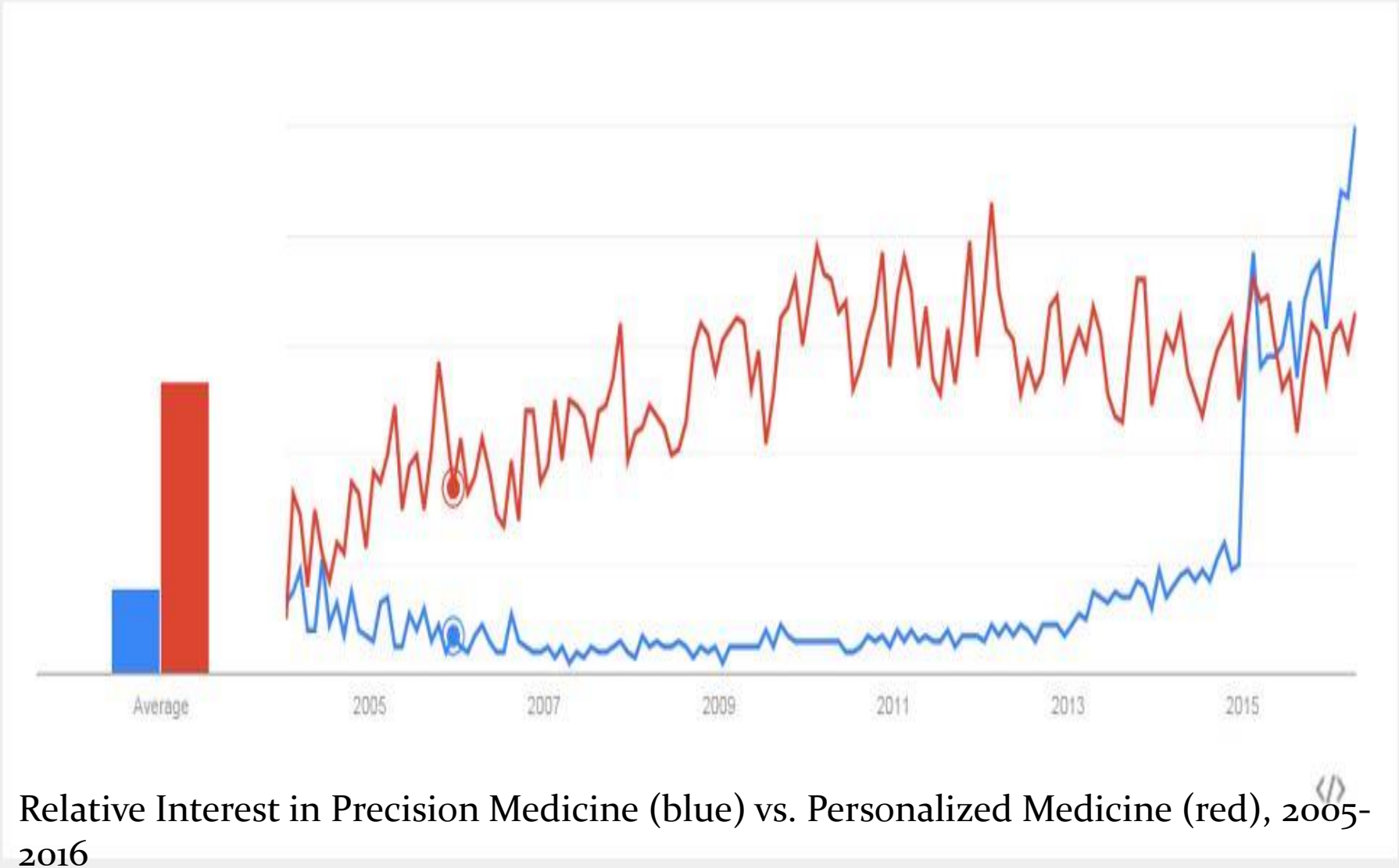
AGENDA

- Precision medicine
- Precision medicine and diabetes mellitus
- Precion medicine and diabetic nephropathy



Relative Interest in Precision Medicine (blue) vs. Personalized Medicine (red), 2005-2016
(Reflected in Google Trend Search on April 10, 2016)

Precision Medicine

- In PM, diagnostic testing is for selecting optimal therapies , based on the context of a patient's genetic content or other molecular or cellular analysis.
- Every person has a unique variation of the human genome.
- Individual's health stems from genetic variation and environment.
- The terms personalized medicine, precision medicine, stratified medicine and P4 medicine are used interchangeably to describe this concept.
- The right treatment, to the right patient, at the right time.

Weiss ST, Implementing Personalized Medicine in the Academic Health Center. J Pers Med. 2016 Sep 21;6(3).

P4 Medicine

A term coined by Dr. Leroy Hood

Personalized	Diagnosis and treatment are customized
Predictive	Determine the risk and outcome
Preventive	Take preventive action according to the risk
Participatory	Patients are involved

Wien Klin Wochenschr (2016) 128 [Suppl 7]:S480–S491

Obama's Precision Medicine Initiative

" Most medical treatments have been designed for the " average patient ". As a result of ' this one- size- fits-all- approach', treatments can be very successful for some patients but not for others."

"Tonight I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes.

And to give us all access to the personalized information we need to keep ourselves and our families healthier."

President Barack Obama

Development of concept

- Human Genome Project (HGP) , determining the DNA sequence of the entire euchromatic human genome , formally launched in 1990 and was complete in 2003.

- Using high throughput technologies, we are now able to perform an exhaustive measurements over a short period of time .

- New technologies and knowledge emerging from HGP , led to the omic revolution in the beginning of the 21th century .

  - Genomic, Transcriptomic , Epigenomic , Proteomic , Metabolomic…

Alyass et al. BMC Medical Genomics (2015) 8:33

Some Facts

- **In human beings, 99.9% bases are same**
- **Remaining 0.1% makes a person unique**
  - Different attributes / characteristics / traits
    - how a person looks
    - diseases he or she develops
- **These variations can be:**
  - Harmless (change in phenotype)
  - Harmful (diabetes, cancer, heart disease, Huntington's disease, and hemophilia)
  - Latent (variations found in coding and regulatory regions, are not harmful on their own, and the change in each gene only becomes apparent under certain conditions e.g. susceptibility to heart attack)

Genomic and GWAS Studies

- To know if a mutation is connected to a certain disease, researchers often do a study called a “genome-wide association study” (GWAS).

- A GWAS study will sequence the genome of many patients with particular disease to look for shared (SNPs) in the genomes.
- SNP : a difference in a single nucleotide and is the most common type of genetic variation among people, threre is roughly 10 million SNPs in the human genome.

- The first GWAS, conducted in 2005, studied patients with age-related macular degeneration.
- Already identified SNPs related to diabetes, heart abnormalities, Parkinson disease, and Crohn disease.

Alyass et al. BMC Medical Genomics (2015) 8:33

omics

- Transcriptome : study of all RNA molecules, produced in one or a population of cells.

  - Transcriptomic analyses have the potential to answer the question of functionality genes discovered in whole-genome studies.

  - Transcriptomes, performed on samples such as bone cells revealing the profiles of about 20,000 expressed genes which may differ in health and disease.

Wien Klin Wochenschr (2016) 128 [Suppl 7]:S480–S491

Omics

- Proteomic studies :

  - Represent the analysis of the gene products.
  - Recognition of proteins differentially expressed between healthy and diseased individuals.

Usually performed by difficult and quite expensive technologies like : 2-DE , MS ,WB .

Wien Klin Wochenschr (2016) 128 [Suppl 7]:S480–S491

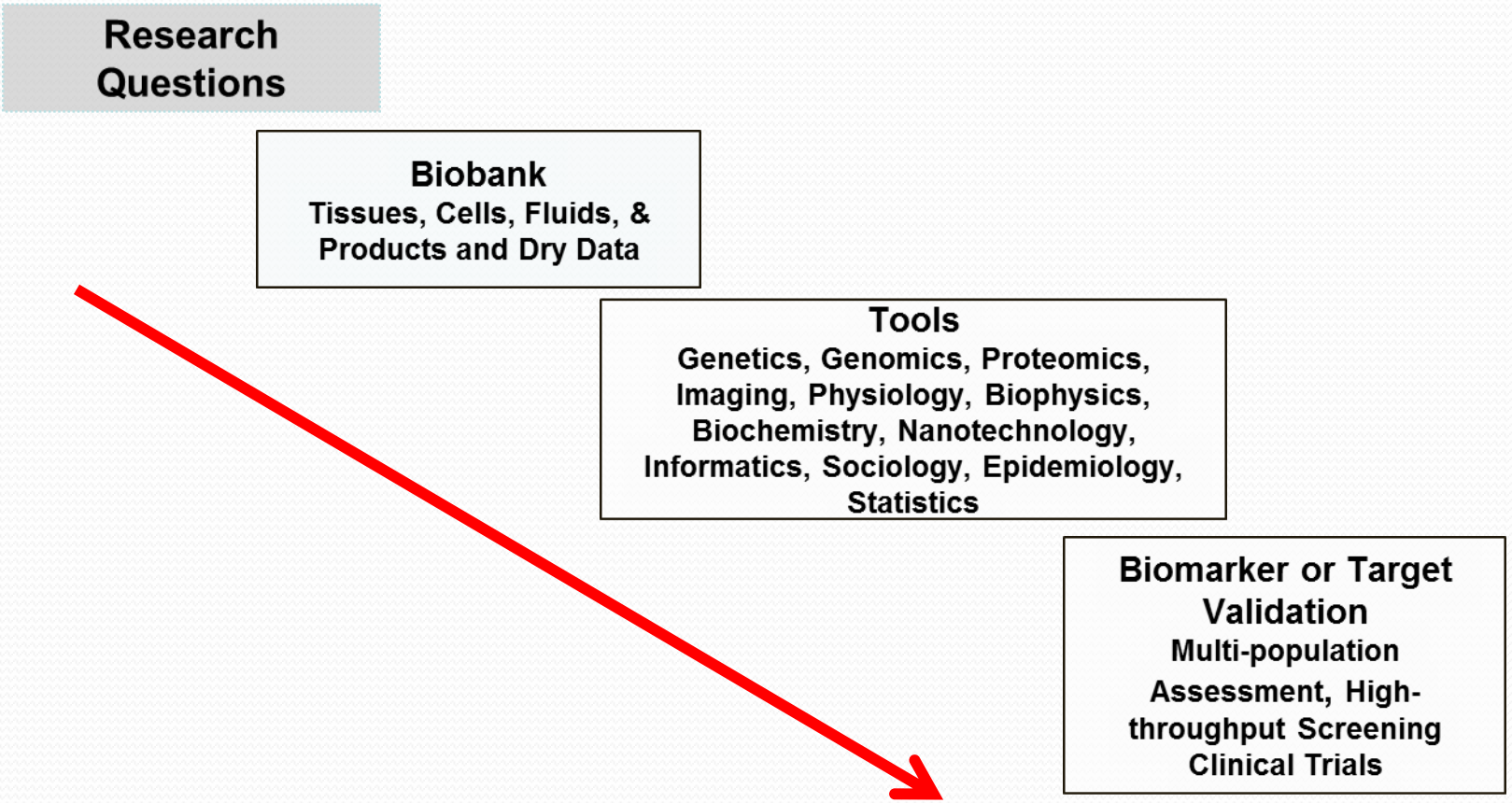
omics

- Metabolomes give us an insight into metabolites that differ between healthy and diseased individuals ,metabolites depend on both genetics and environment.
  - The small changes in gene and protein could be amplified in the metabolic level.

- Pharmacogenomics combines pharmacology and genomics , study of the role of genetic in drug response,..

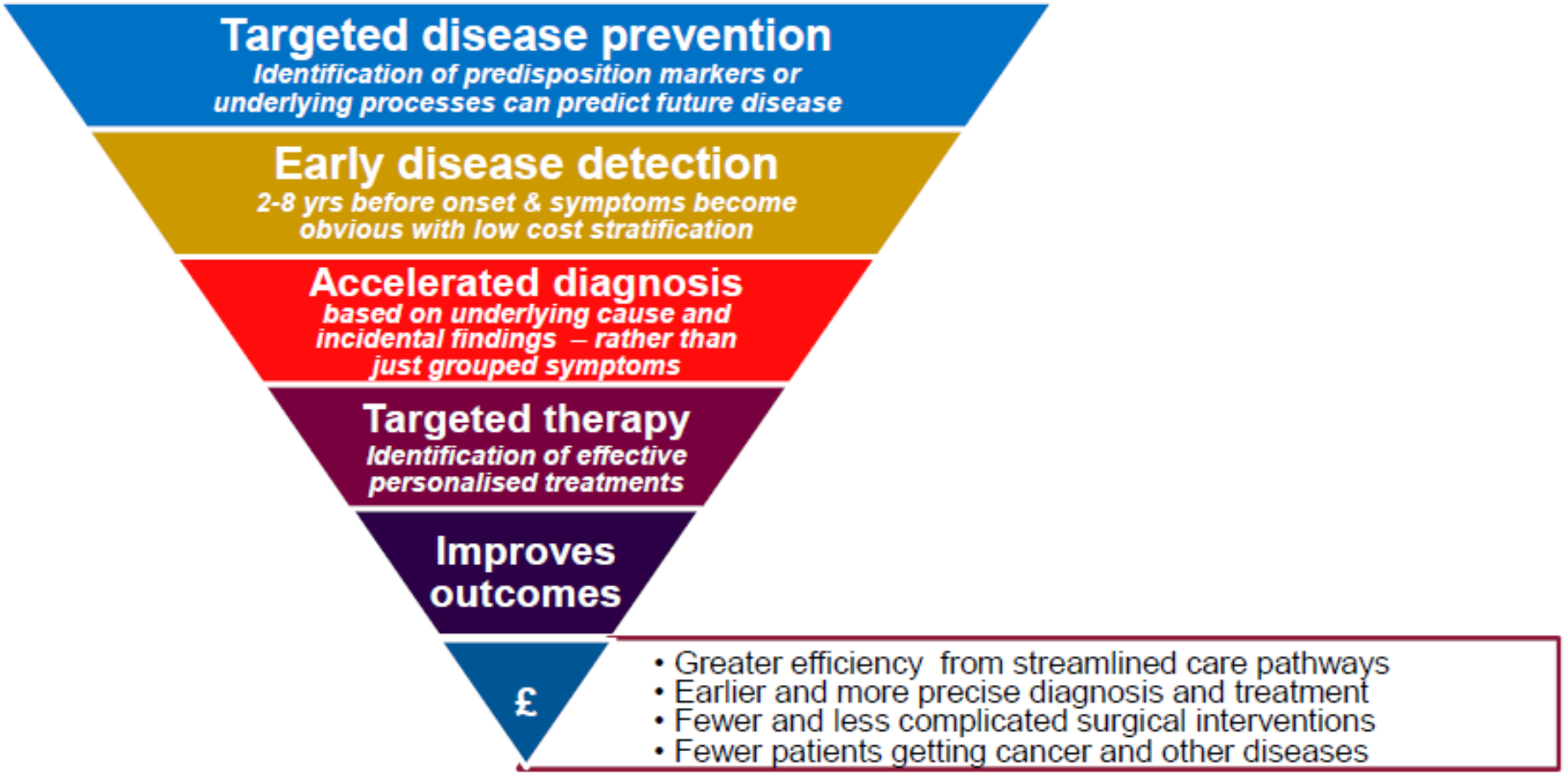
Wien Klin Wochenschr (2016) 128 [Suppl 7]:S480–S491

The Personalized Medicine Research Cycle from Bench to Bedside



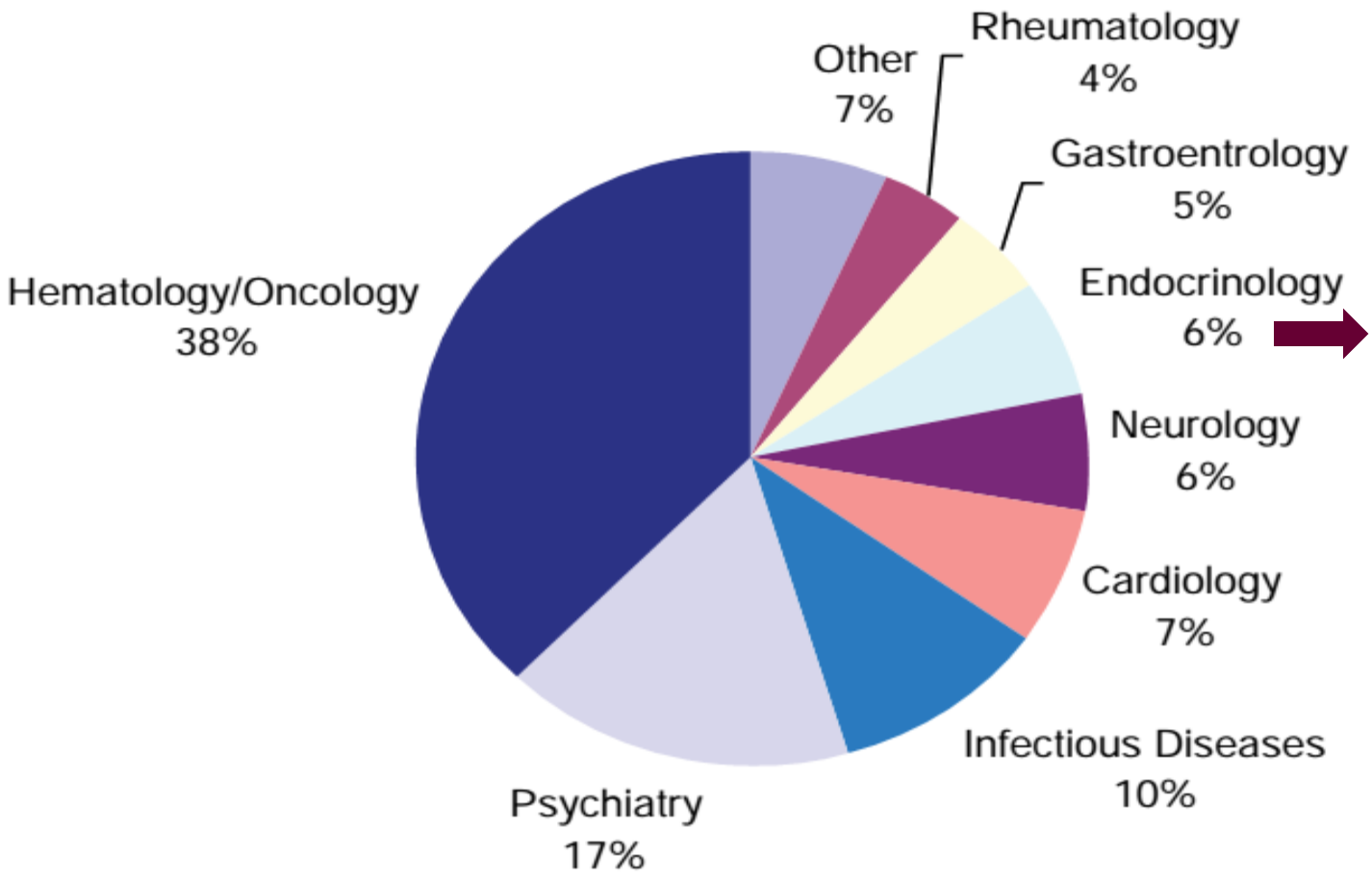
Improving outcomes through personalisation

NHS England



Diabetes care has remarkable growth whereas oncology pioneered the introduction of precision treatment based on genetics

Pharmacogenomic Biomarker Information in Drug Labeling

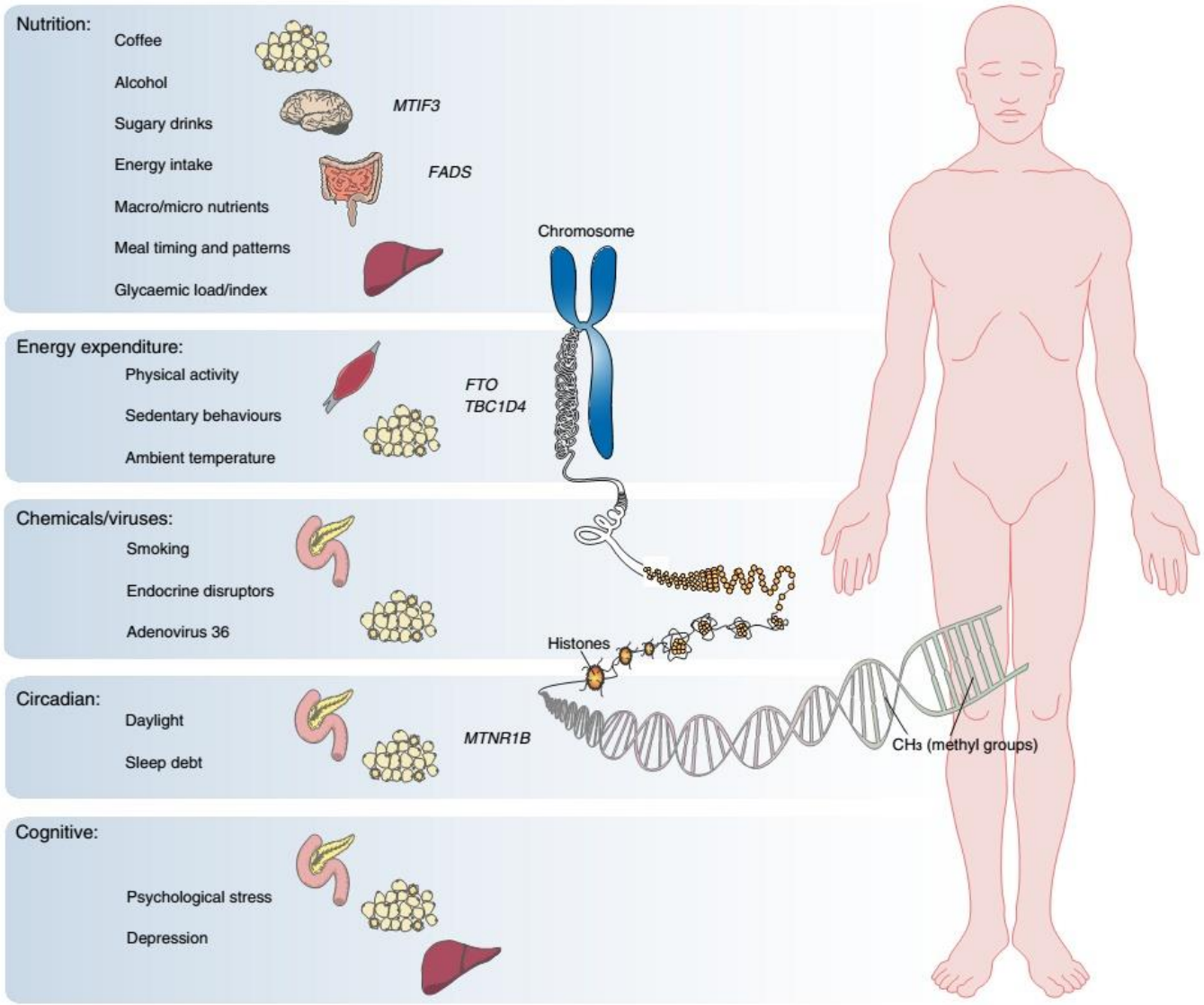


Alirocumab, LDLR
Carglumic Acid, NAGS
Chlorpropamide, G6PD
Cholic Acid, AKR1D1, HSD3B7, CYP27A1, AMACR, CYP7A1
Eliglustat, CYP2D6
Elosulfase, GALNS
Evolocumab, LDLR
Glimepiride ,Glipizide and Glyburide, G6PD
Lomitapide, LDLR
Mipomersen, LDLR
Pravastatin, LDLR
Rosuvastatin, SLCO1B1

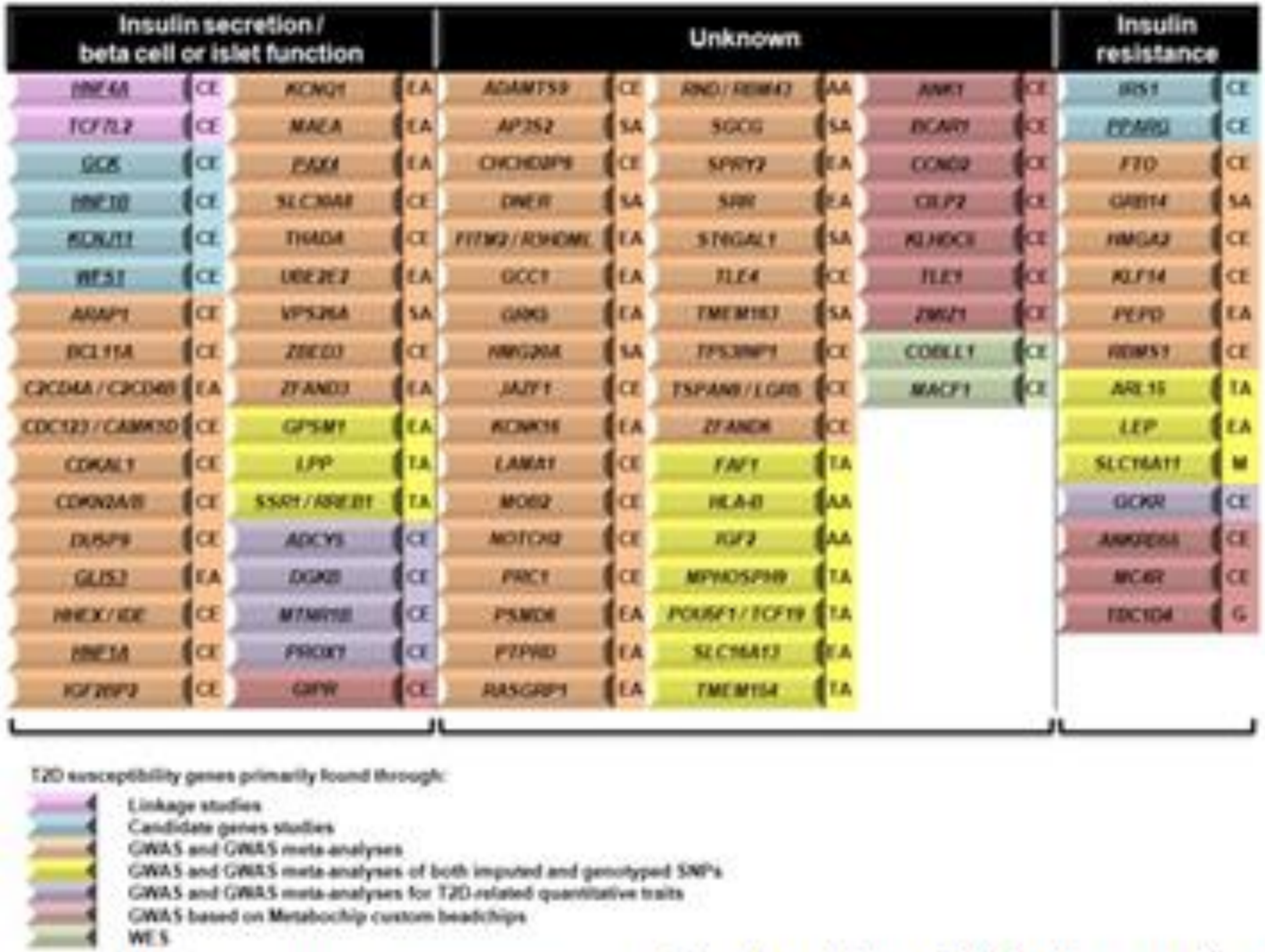
Paving the Way for Personalized Medicine, FDA's Role in a New Era of Medical Product Development


افسردگی
38%
آسم
40%
آریتمی قلبی
40%
دیابت
43%
میگرن
48%
آرتریت
50%
پوکی استخوان
52%
آلزایمر
70%
سرطان
75%

Type 2 diabetes results from the complex interplay between environmental and genomic factors



Type 2 Diabetes Genetics



Bonnefond and Froguel (2015) Cell Metabolism 21:357

Check out: type2diabetesgenetics.org

Why Personalized medicine for T2DM

- In tight glycemic control, some individuals develop complications,
- Others with poor control seem to not develop complications.
- Patients with impaired glucose tolerance are at greater risk for macrovascular complications than those with impaired fasting glucose

Why Personalized medicine for T2DM

- Prediabetes identification (ADA)
  1. Fasting plasma glucose (FPG) of 100– 125 mg/dL (impaired fasting glucose)
  2. Plasma glucose 2 hours after a 75-g oral glucose challenge of 140–199 mg/dL (impaired glucose tolerance)
  3. Hemoglobin A1c (HbA1c) test of 5.7%–6.4%.

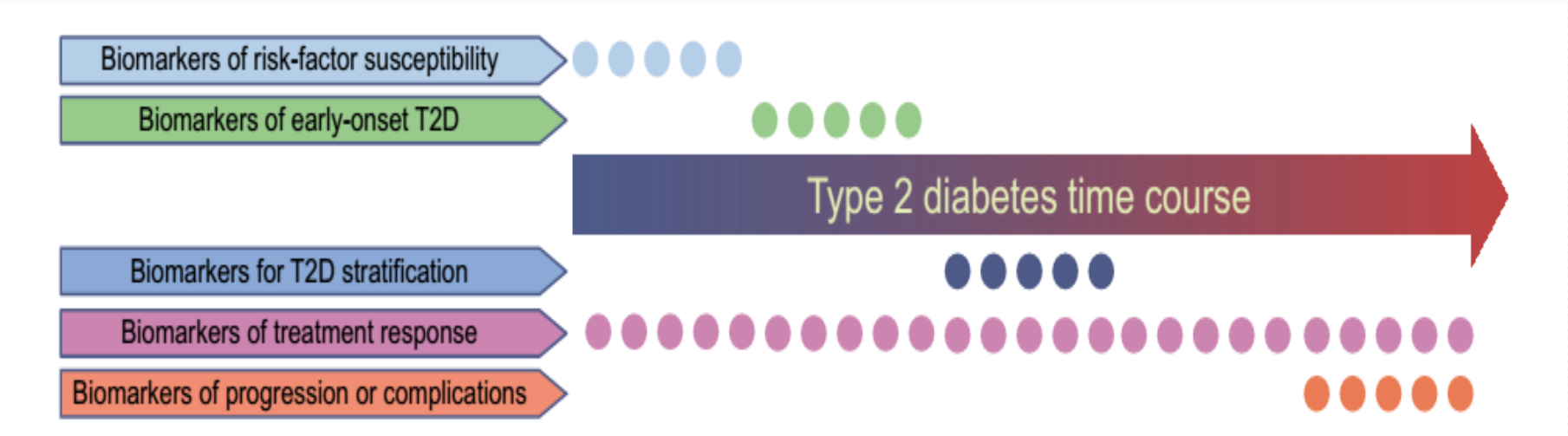
Why Personalized medicine for T2DM

Problem ….!??!

These criteria do not identify identical groups of people at increased risk for DM2,
and their pathophysiology and susceptibility to complications

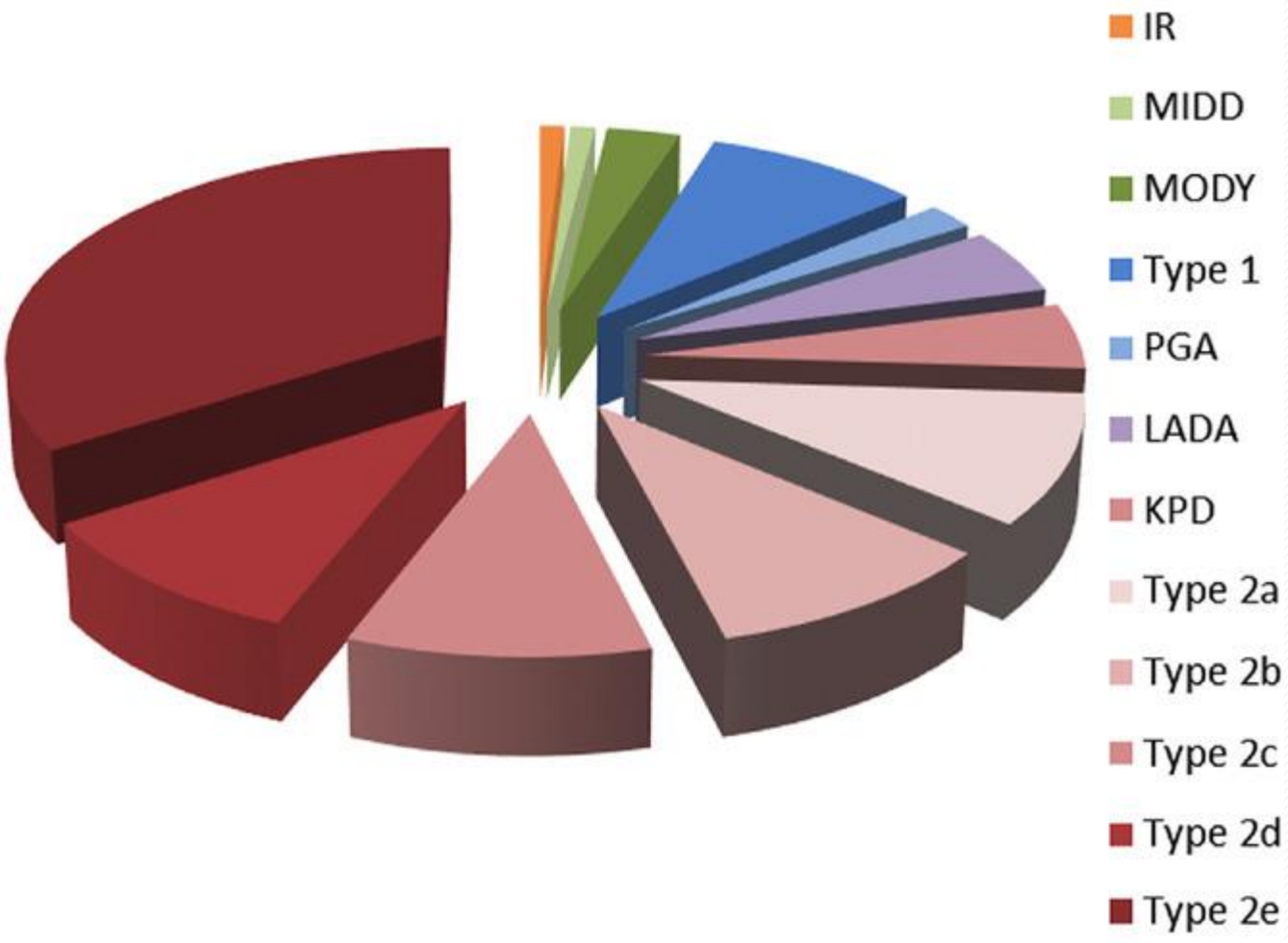
So We need PERSONALIZED MEDICINE FOR T2DM

Precision Medicine T2DM Time Course



A schematic showing key time points for intervention in the course of type 2 diabetes pathophysiology where precision lifestyle medicine might play a role

Lifestyle and precision diabetes medicine: will genomics help optimise the prediction, prevention and treatment of type 2 diabetes through lifestyle therapy? Diabetologia, 5 October 2016


IR
MIDD
MODY
Type 1
PGA
LADA
KPD
Type 2a
Type 2b
Type 2c
Type 2d
Type 2e

Many important resources for precision diabetes medical research have been launched.

- NIH and pharmaceutical companies with the aim of precision preventive and treatment , collected the results from 28 large (GWAS)

  (www.type2diabetesgenetics.org)

- (IRAS) by supporting of (NHLBI) have found a possible biomarker for the incidence of T2DM (16).

search for the genetic basis of T2DM

- GWAS studies: >150 risk alleles
  - Responsible for only 10% of the variation in T2DM tendency (53,54).
  - Most of them encode intracellular proteins that mediate the secretion of insulin from beta cells.

- Linkage study : A susceptibility gene, which has been found was TCF7L2

- Candidate gene approach : The association of PPARG and KCNJ11- ABCC8 with T2DM have been found (47).

Diabetes Complications

- Occurrence and progression of diabetes complications are influenced by:
  - Modifiable risk factors , such as HTN and HLP.
  - Non modifiable risk factors : genetic predisposition variants. (58).

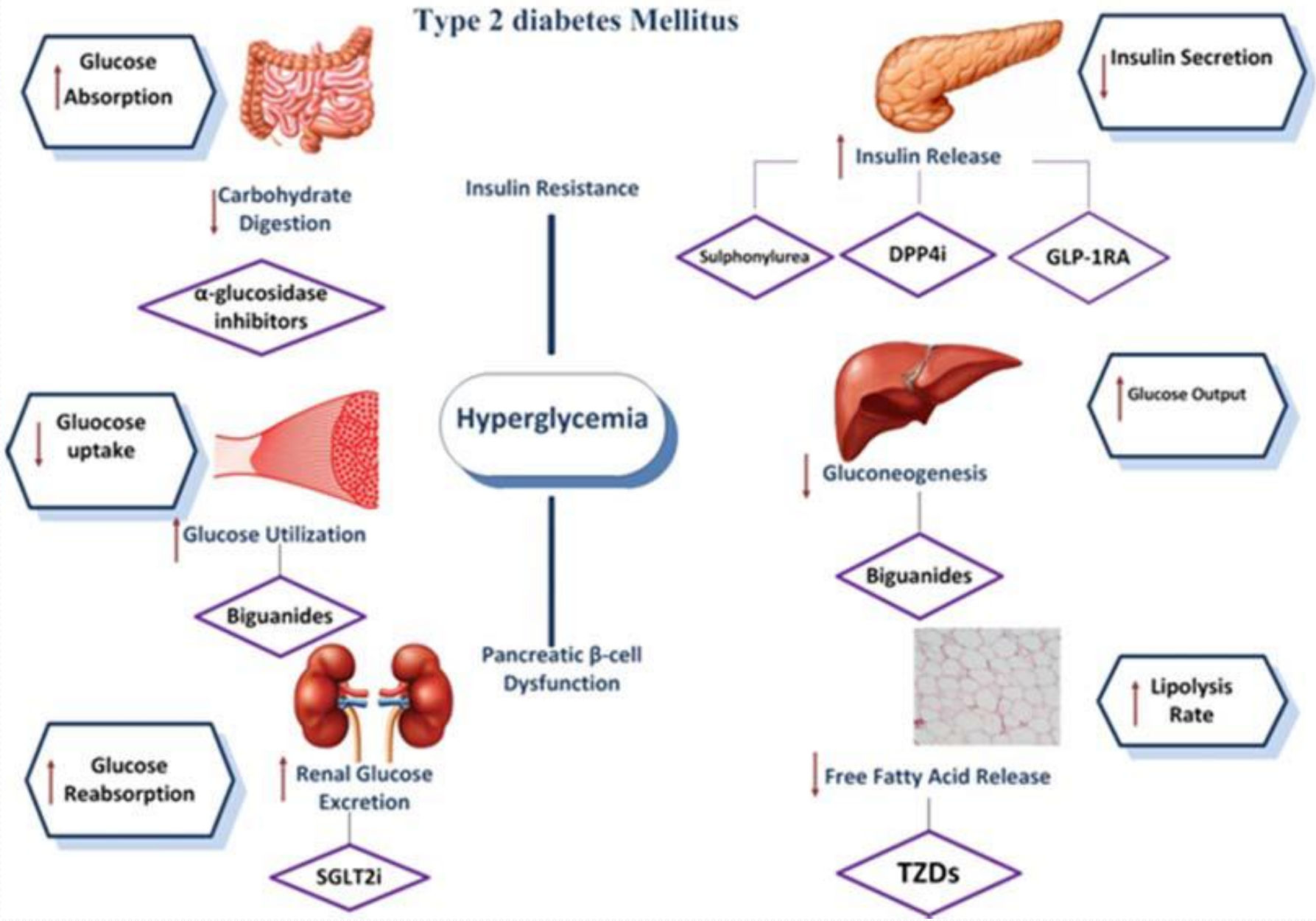
- GWAS in (ACCORD) trial in patients with T2DM , under intensive glycemic therapy, two genetic variants (*rs9299870, rs57922 on chromosome 10 and 5)* predict the cardiovascular effects (56).

After 15 to 2o years diagnosis of DM:

- 50%- 80% of patients show retinopathy(two candidate genes VEGFA and AKR1B1)

- 30% have shown an early stage of nephropathy(A well-known GWAS for DKD is related to variation in the gene encoding ACE.

Management of T2DM from a pathophysiological point of view

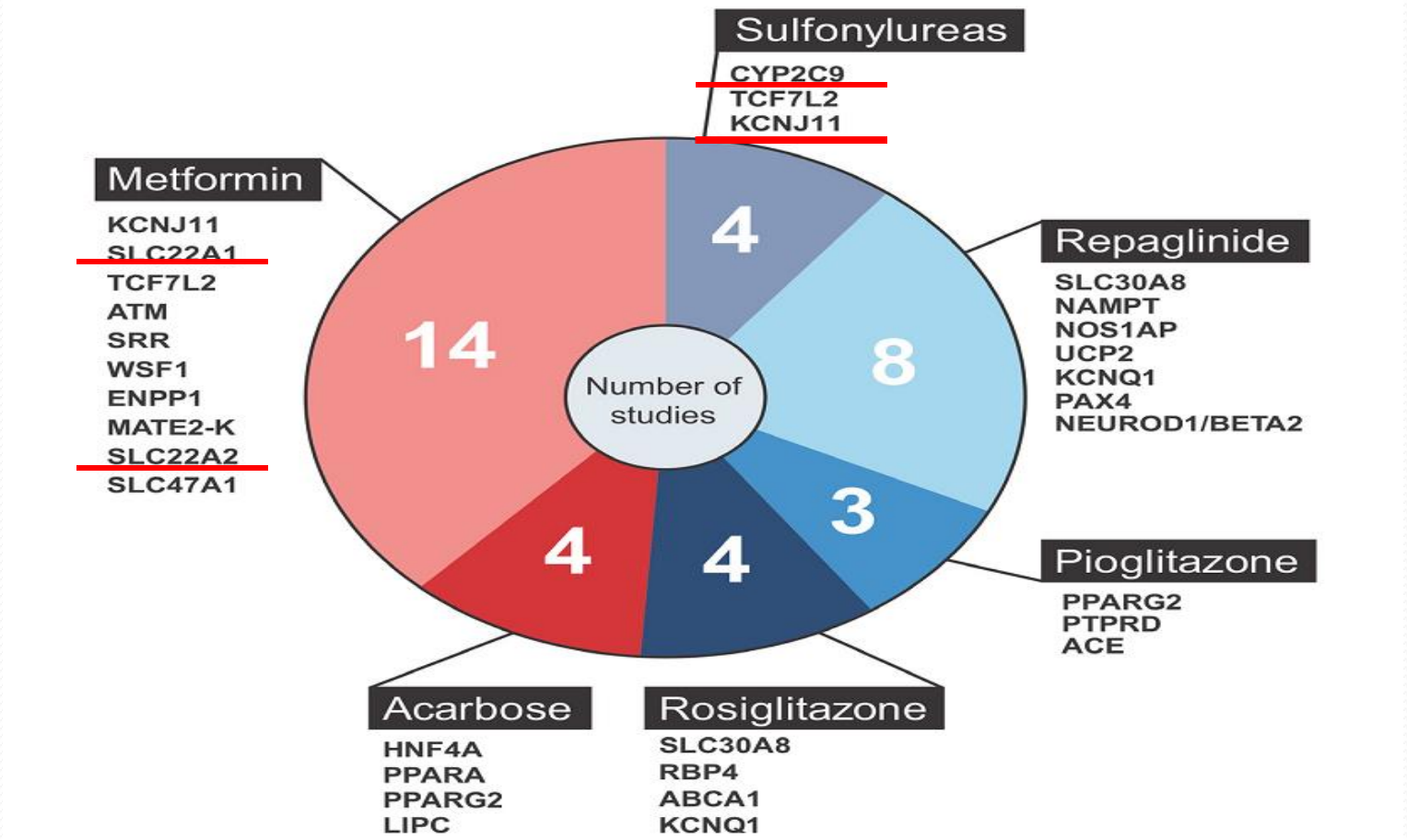


- An essential concern on pharmacogenomic studies is the genetic makeup of drug response

- The pharmacokinetic approach is focused on some candidate genes related to:
  - Drug targets
  - Drug metabolism
  - Drug distribution

- Few strong pharmacogenetics studies have been done in DM treatment

Regulatory genes in significant gene–drug interaction for anti-diabetic medication



Kaixin Zhou,Pharmacogenomics in diabetes mellitus: insights into drug action and drug Discovery. Nature Reviews Endocrinology 12, 337–346 (2016)

In spite of newly recognized diabetes molecular pathways, there is a large gap between molecular knowledge of diabetes and using it in the clinic or at the bedside.

DKD

- Mechanistic heterogeneity of diabetic kidney disease (DKD) causes reduced capability to identify risk variants. Some risk variants from APOL1, UMOD genes have been reported, and APOL1 is independent of diabetes status. A well-known GWAS for DKD is related to insertion/deletion (I/D) variant in the gene encoding ACE.

Conclusion & future perspective

The ideal of personalized care is that each patient receives the management plan best suited to him or her.

This means implementinga treatment strategy that is concordant with the patient's preferences, specific risks and unique underlying disease pathophysiology anddrug metabolism profile. Although the benefit

remains to be proven, such an approach holds the potential to substantially improve the care of patients with Type 2 diabetes.

Thank you for Attention