# Dalla terapia personalizzata alla diabetologia di precisione


## Francesco Dotta

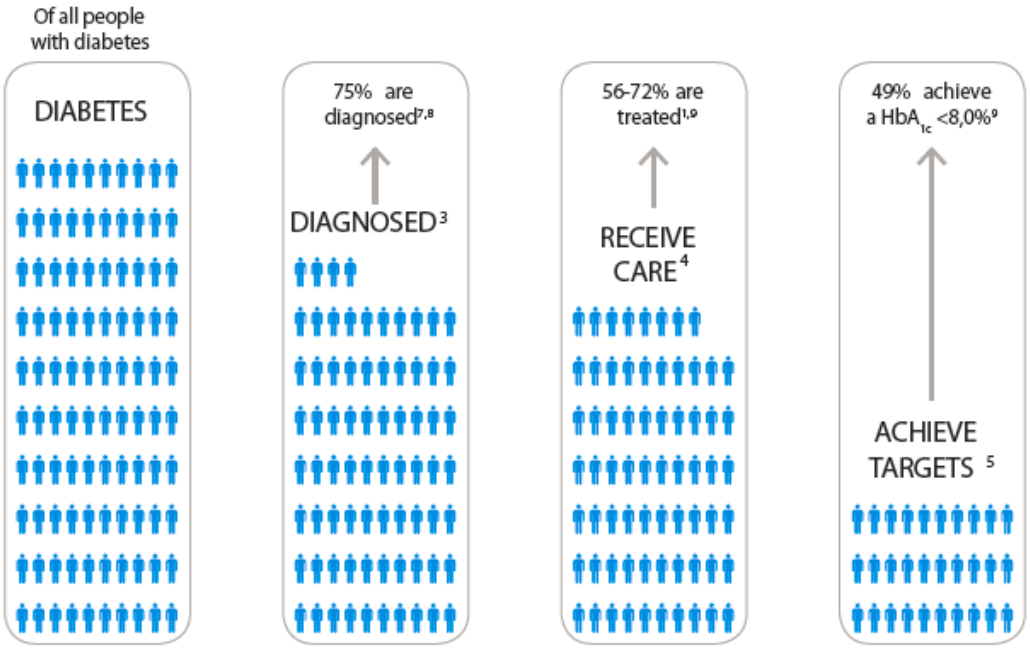
**UOC Diabetologia, Azienda Ospedaliera Universitaria Senese;**
**Dip. Scienze Mediche, Chirurgiche e Neuroscienze, Università di Siena;**

**Fondazione Umberto Di Mario ONLUS**
**Toscana Life Science Park, Siena**

**Il sottoscritto Prof. Francesco Dotta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:**

- **Astra Zeneca**
- **Eli Lilly**
- **GlaxoSmithKline**
- **Johnson & Johnson**
- **Merck Sharp & Dohme**
- **Novo Nordisk**

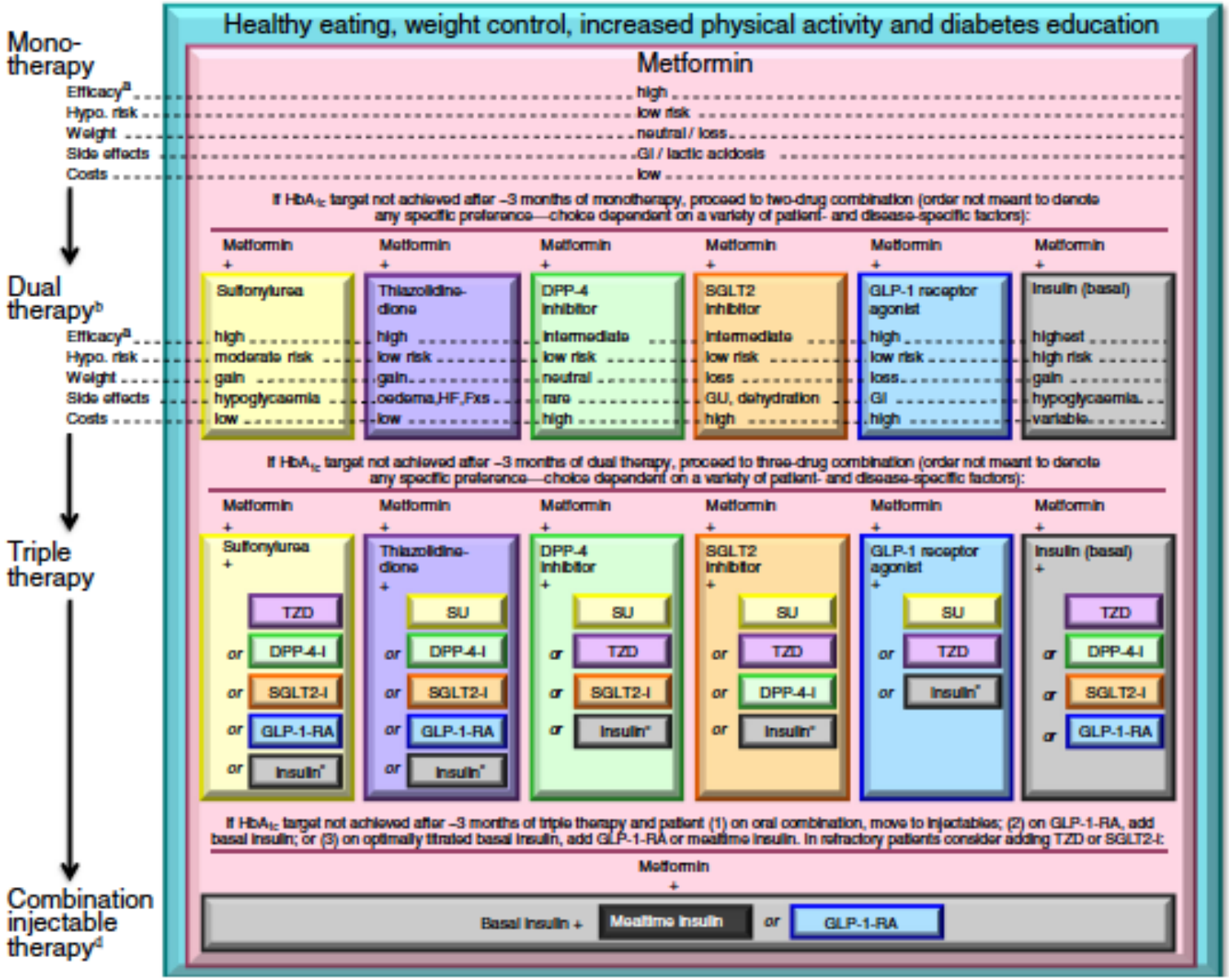
# DIAGNOSIS AND TREATMENT ARE NOT OPTIMAL




A large part of the diabetes population remains undiagnosed or does not receive pharmacological treatment. Early and effective treatment of diabetes can help to reduce the risk of long-term complications.

1 VII Report Health Search, Available at: http://healthsearch.it/documenti/Archivio/Report/VIIReport_2011-2012/VII%20Report%20HS.pdf
7 . HealthSearch, data on file.
8- Screening campaign, health district of Siena. Data on file
9. AMD Annals 2011/2012, available at: http://www.infodiabetes.it/files/Annali%202011%20def.pdf

Italian Barometer Diabetes Observatory
Principiis Obsta
Foundation




*Diabetes Care, Diabetologia.* 2015

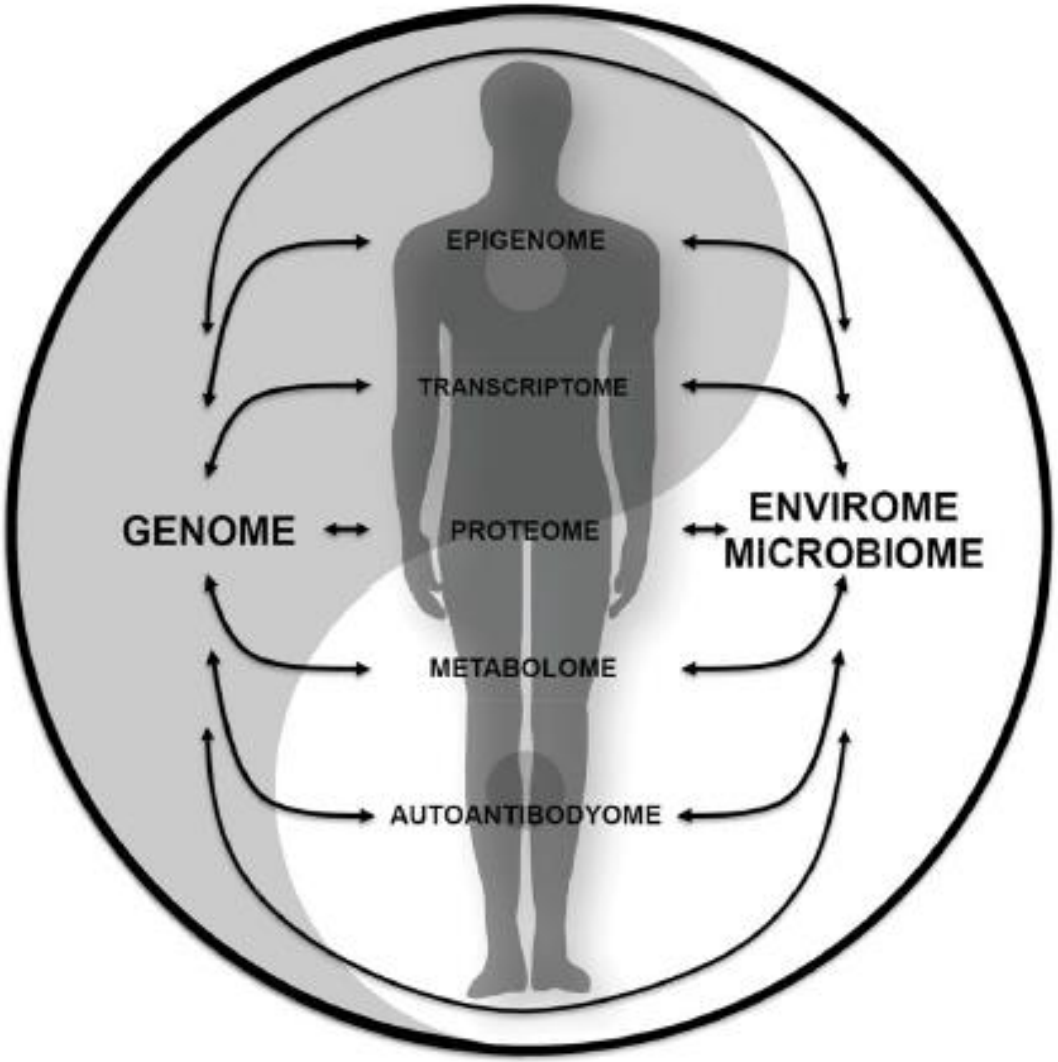
# La prossima sfida per la Diabetologia:

# La "Precision Medicine"

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

— President Barack Obama, State of the Union Address, January 20, 2015

N ENGL J MED 372;9 NEJM.ORG FEBRUARY 26, 2015



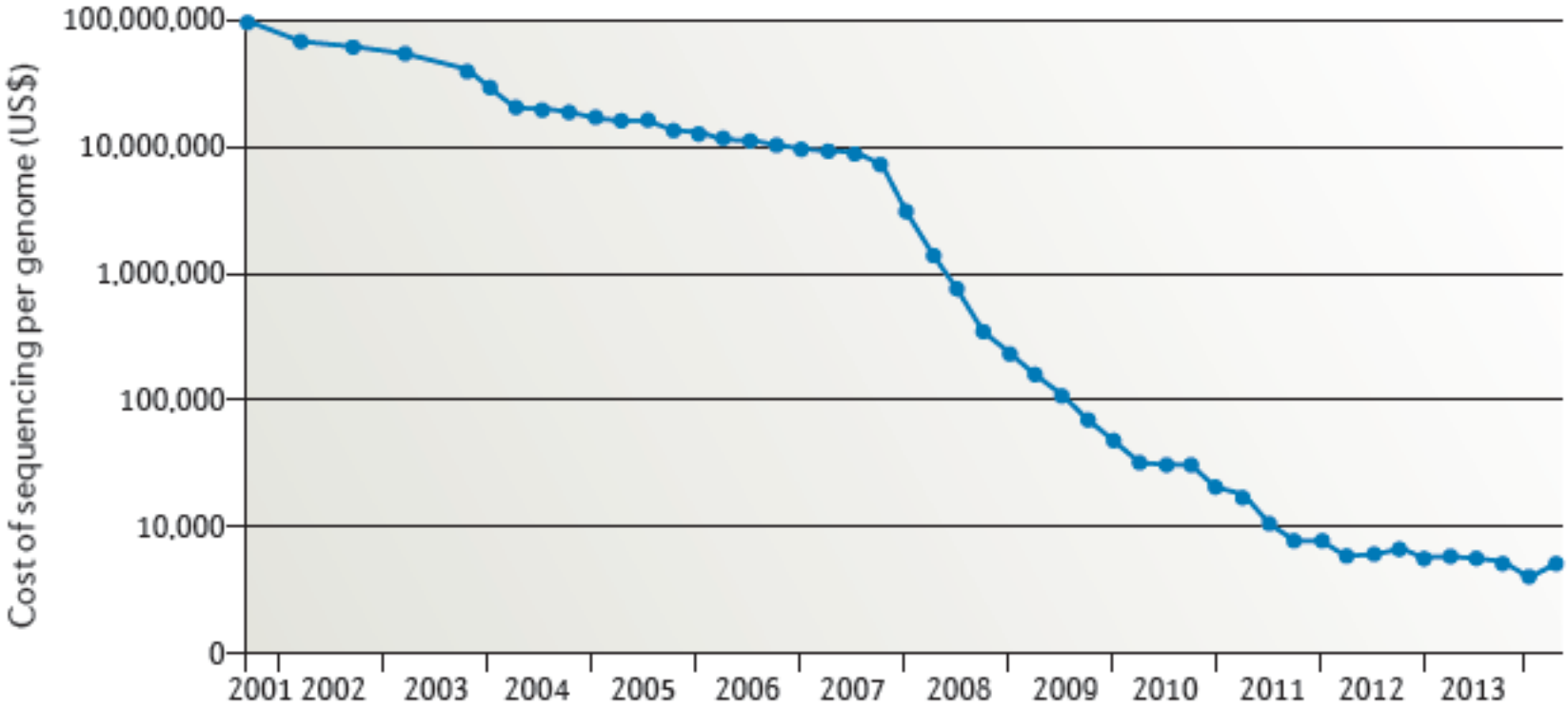

Si può parlare di nuova era della **Precision Medicine** perché oggi possiamo contare su:

✓Database biologici su larga scala;

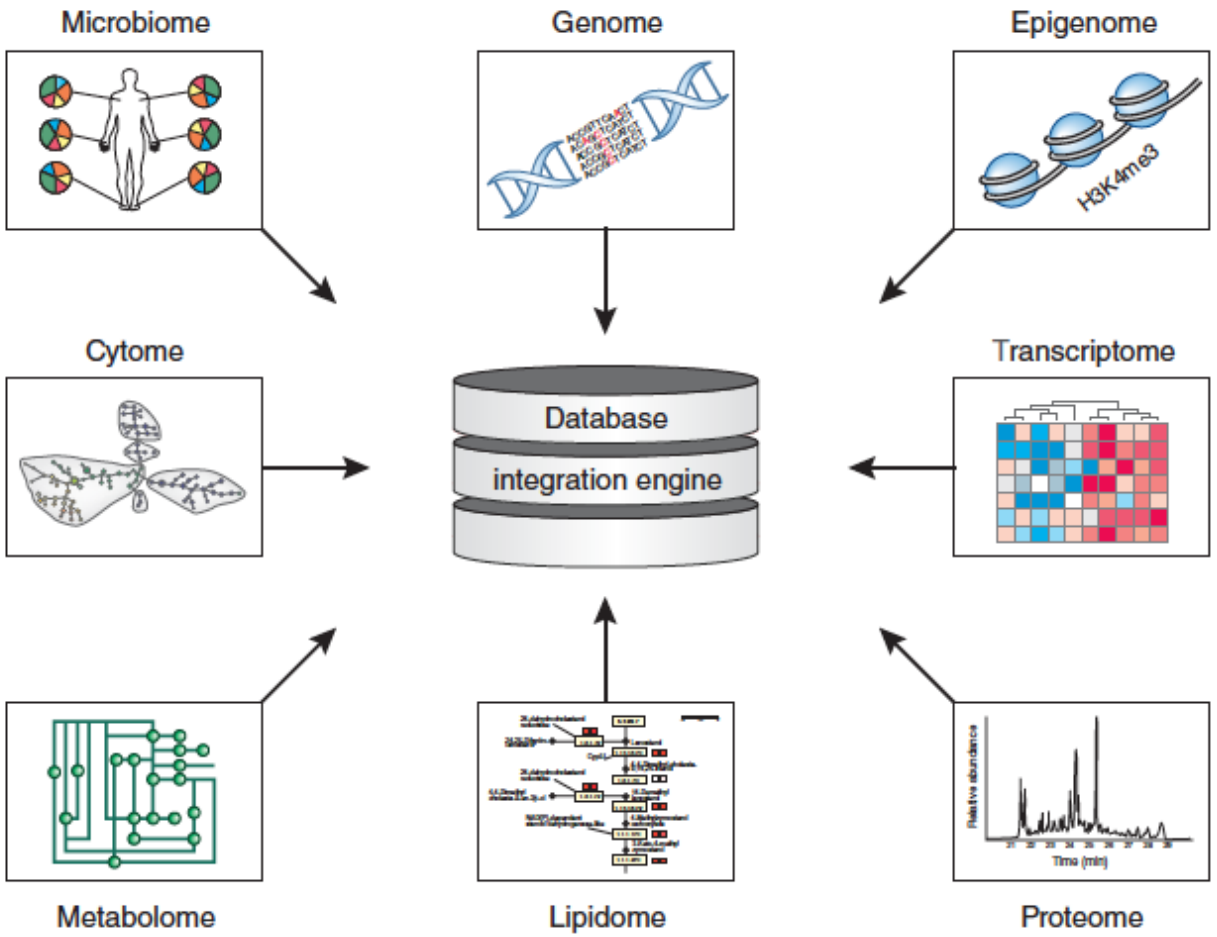
✓Potenti strumenti di caratterizzazione "omica" del paziente;

✓Strumenti informatici per la gestione di *Big Data*;

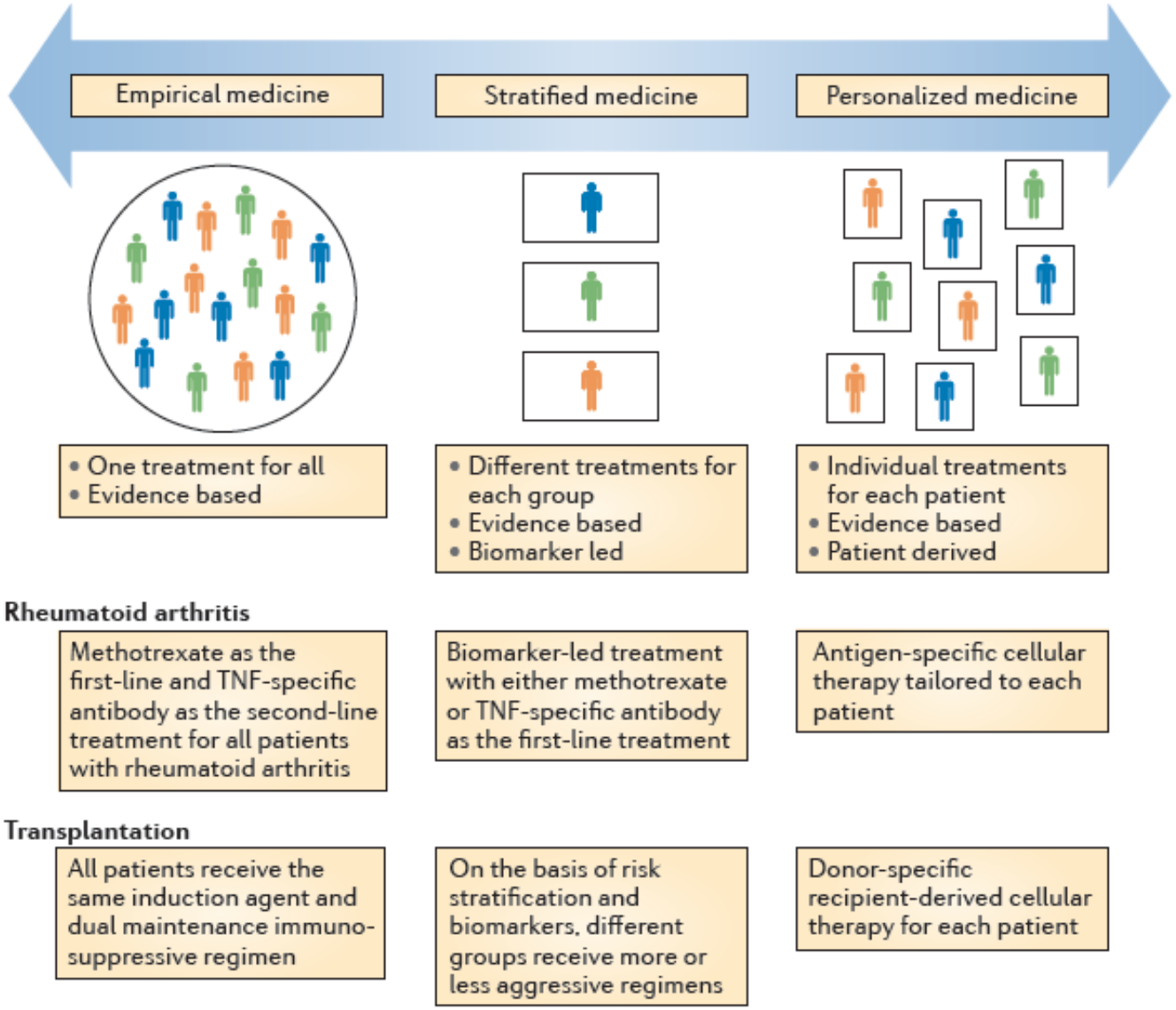
# Il costo per sequenziare un genoma




Nat.Rev.Immunol., doi:10.1038/nri3820 , March 2015



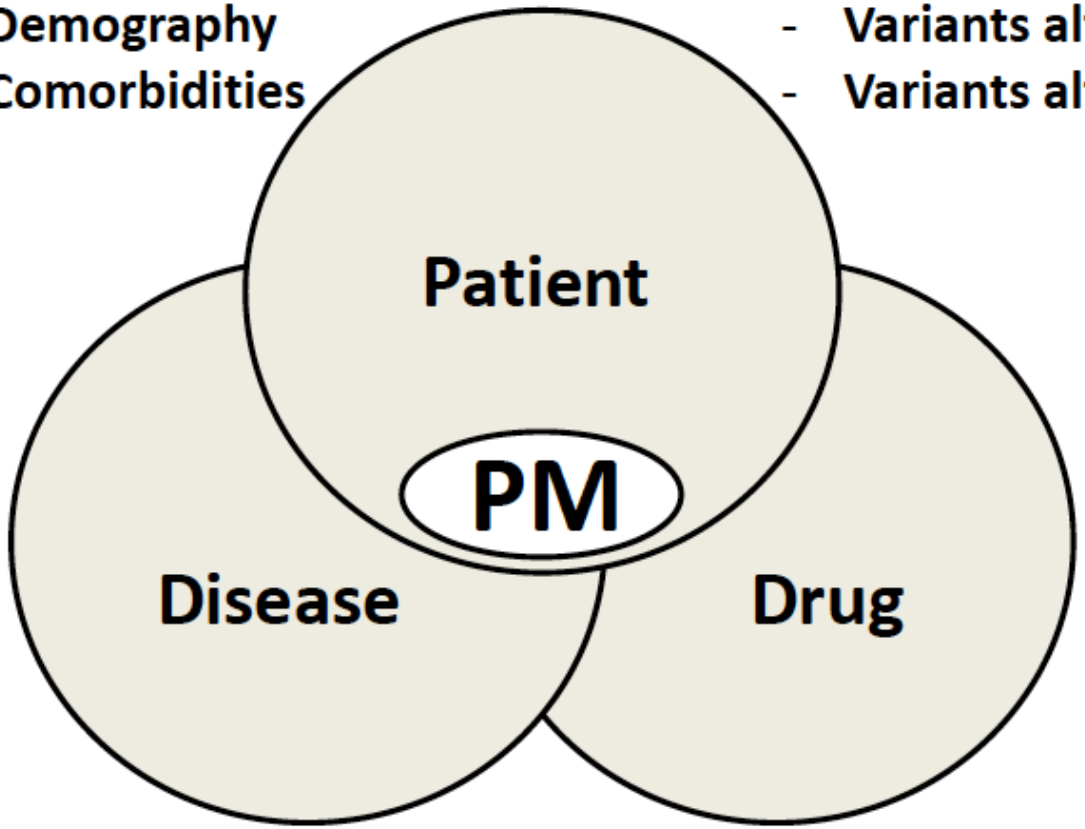

Nat.Rev.Immunol., doi:10.1038/nri3820 , March 2015


Empirical medicine
Stratified medicine
Personalized medicine
• One treatment for all
• Evidence based
• Different treatments for each group
• Evidence based
• Biomarker led
• Individual treatments for each patient
• Evidence based
• Patient derived
Rheumatoid arthritis
Methotrexate as the first-line and TNF-specific antibody as the second-line treatment for all patients with rheumatoid arthritis
Biomarker-led treatment with either methotrexate or TNF-specific antibody as the first-line treatment
Antigen-specific cellular therapy tailored to each patient
Transplantation
All patients receive the same induction agent and dual maintenance immuno-suppressive regimen
On the basis of risk stratification and biomarkers, different groups receive more or less aggressive regimens
Donor-specific recipient-derived cellular therapy for each patient

# Precision medicine: the future in diabetes care ?

**Phenotype**
- Demography
- Comorbidities

**Genotype**
- Variants altering PK
- Variants altering PD

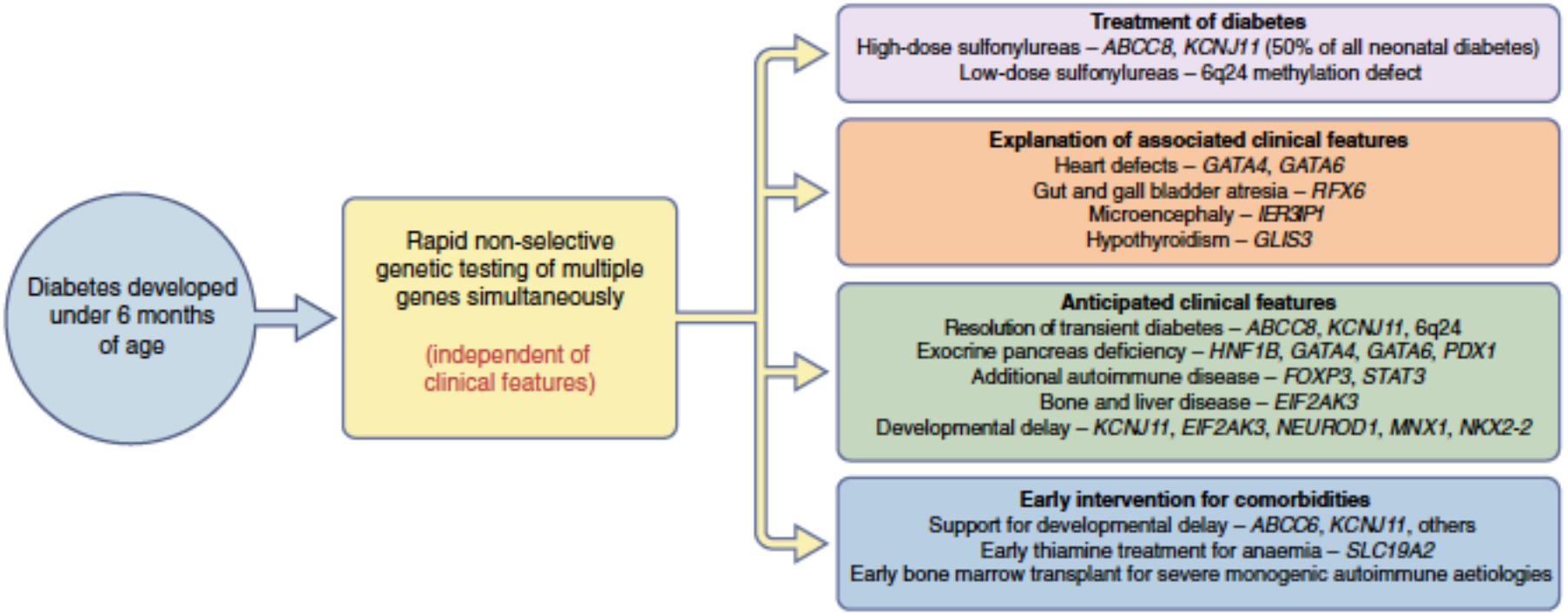



- Duration
- Severity (HbA1c)
- Fasting/postprandial
- Insulin secretion/resistance

- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Cost

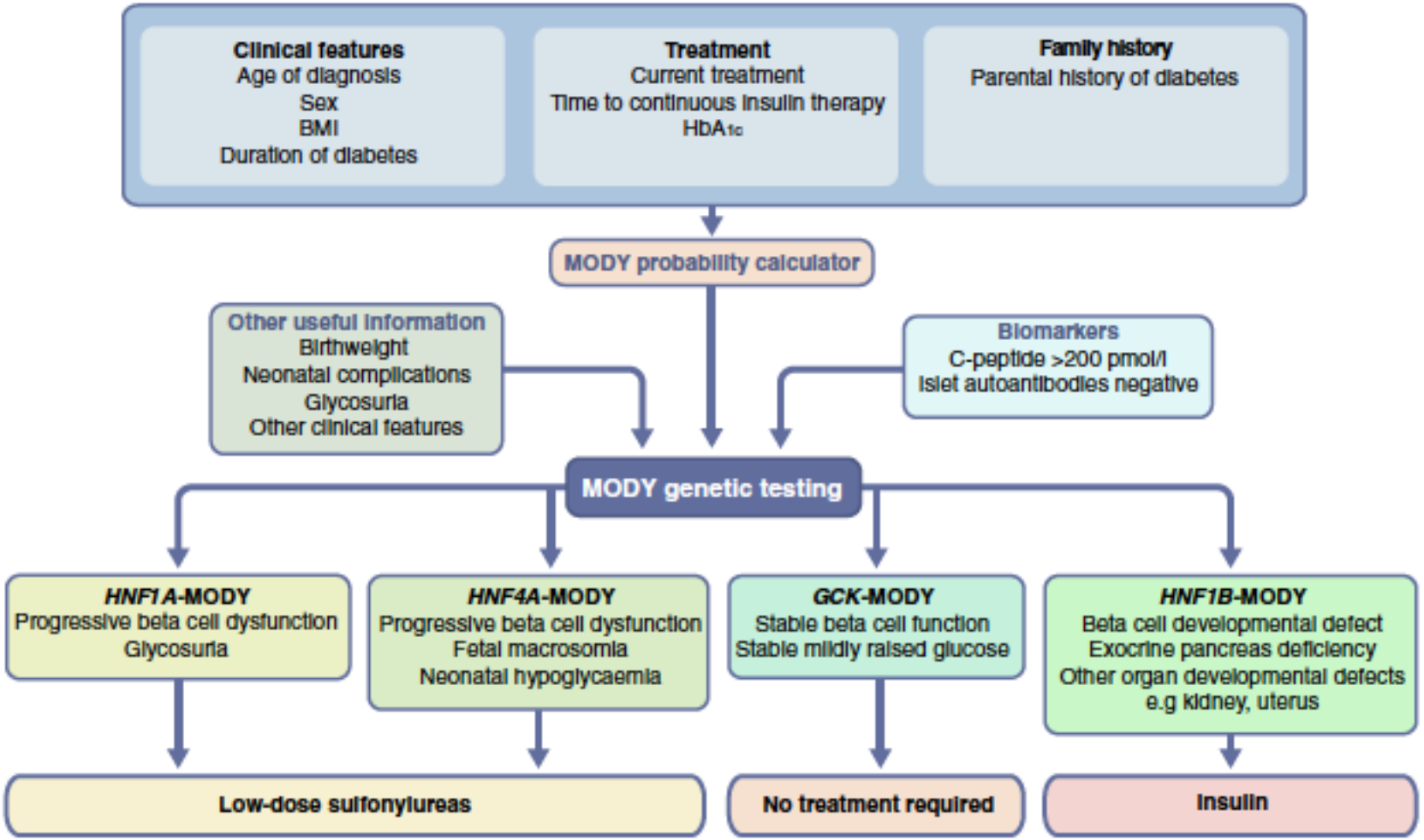
Diab Res Clin Pract. 2016, 117: 12–21

# Precision diabetes: learning from monogenic diabetes



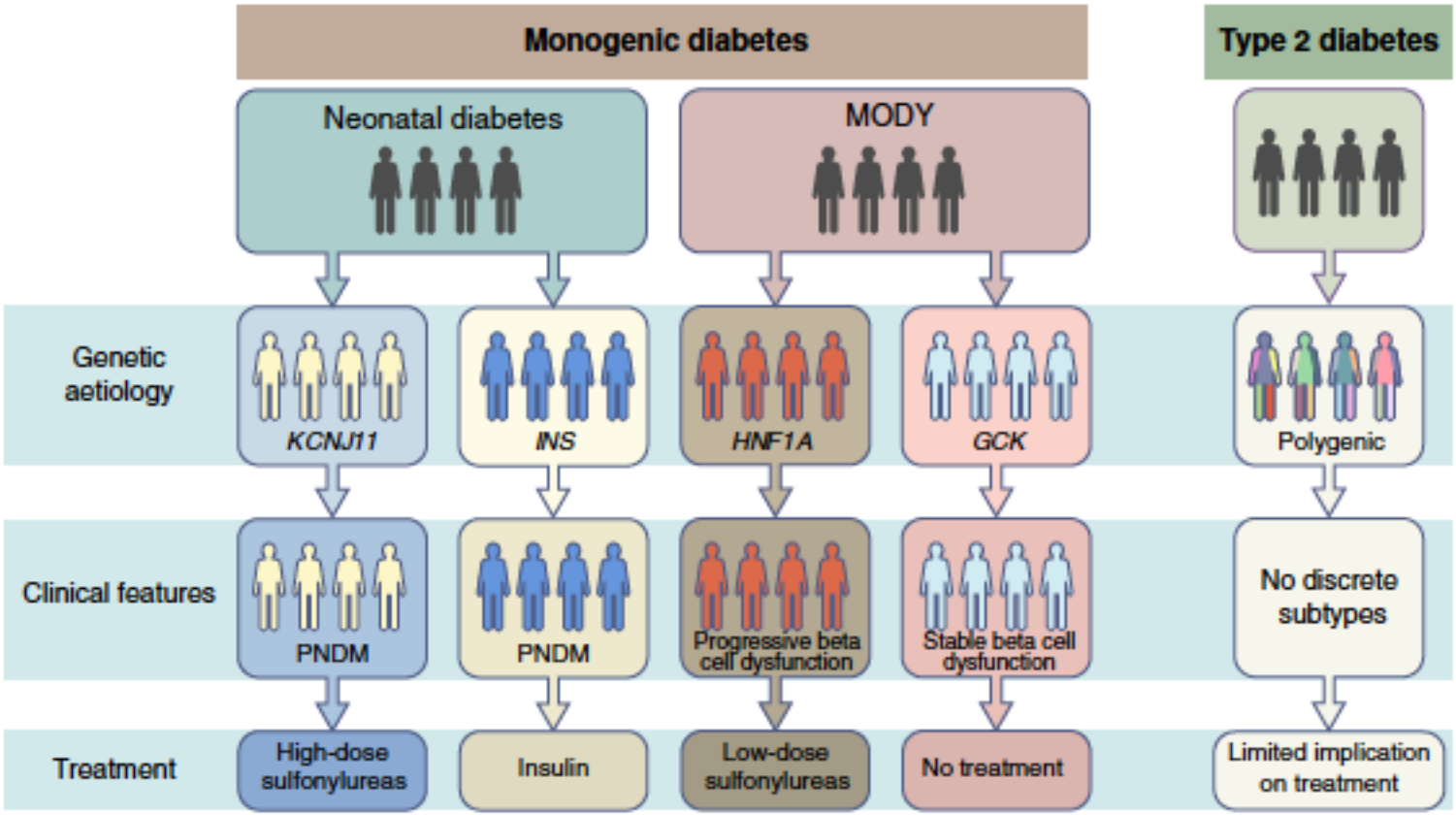

Diabetologia (2017) 60:769–777

# Precision diabetes: learning from monogenic diabetes




Diabetologia (2017) 60:769–777

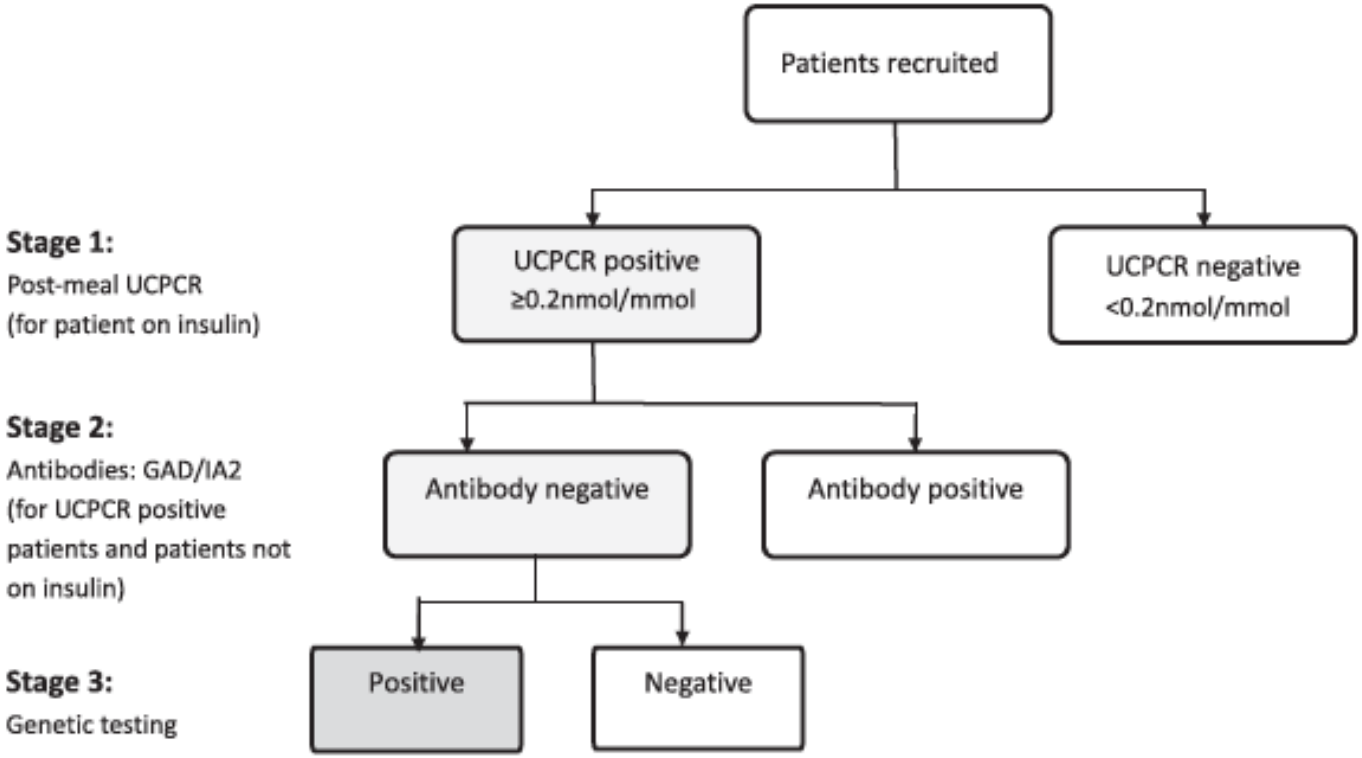
# Precision diabetes: learning from monogenic diabetes



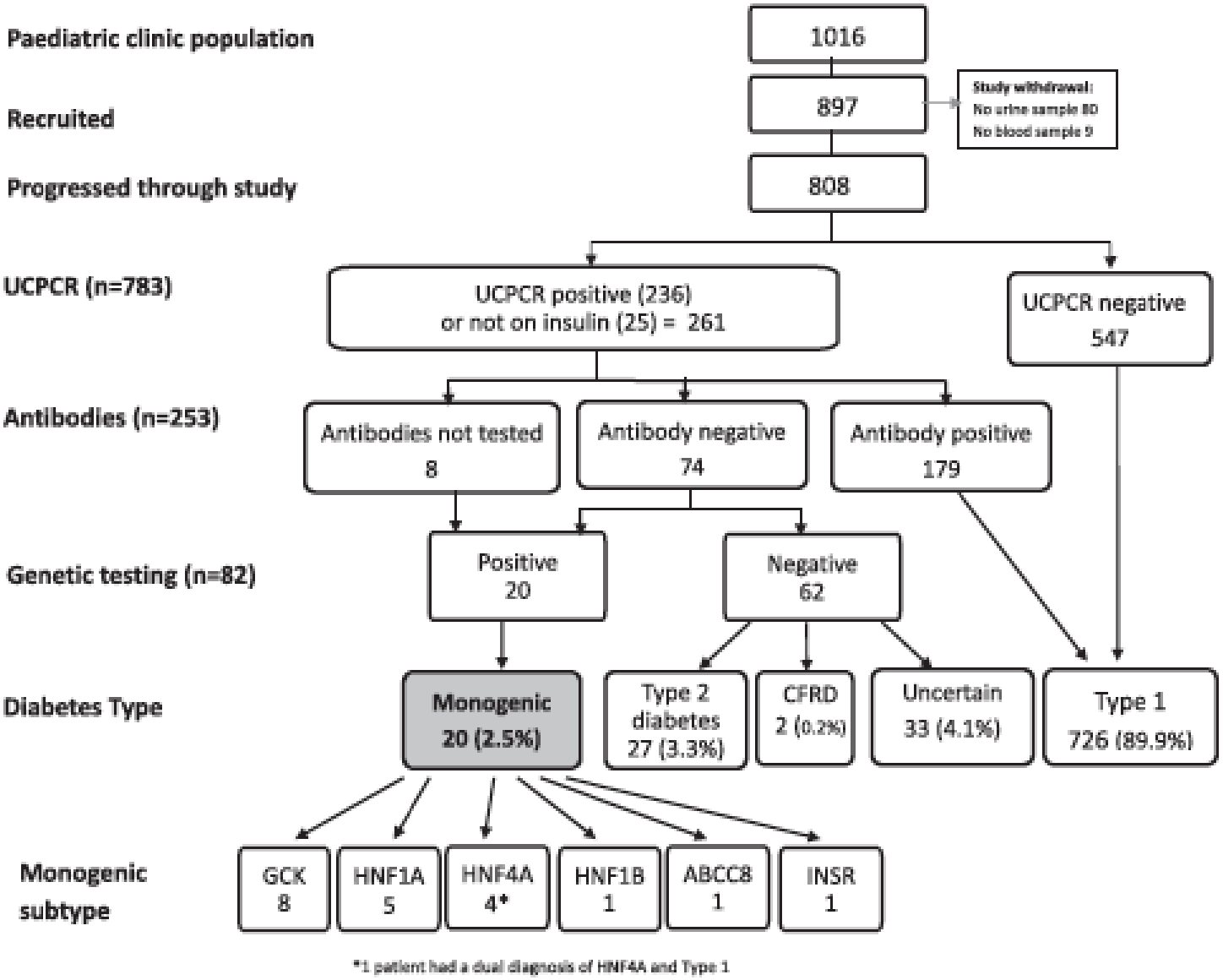

Diabetologia (2017) 60:769–777

# Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes

**Diabetes Care**

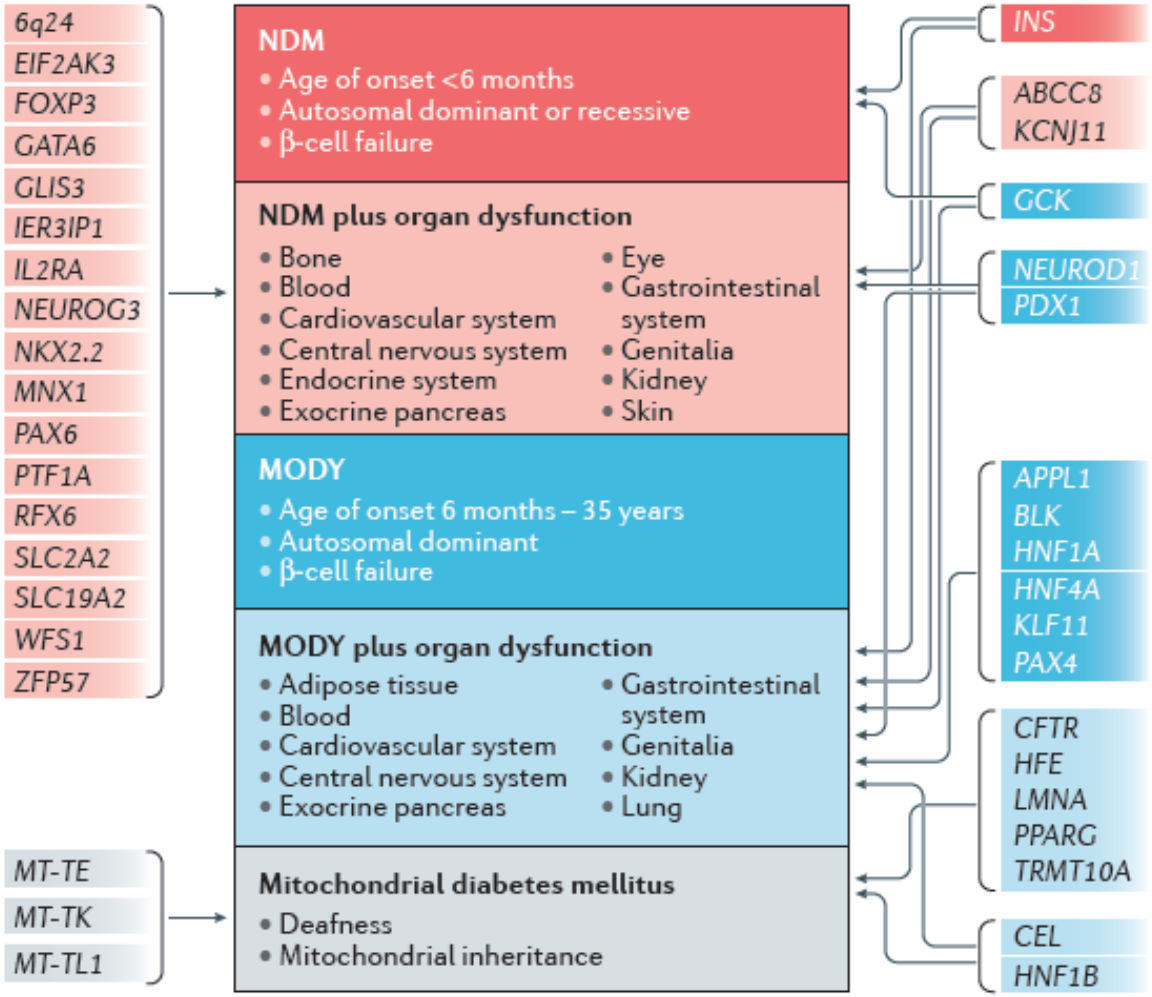


# Screening for MODY in UK diabetic pediatric population



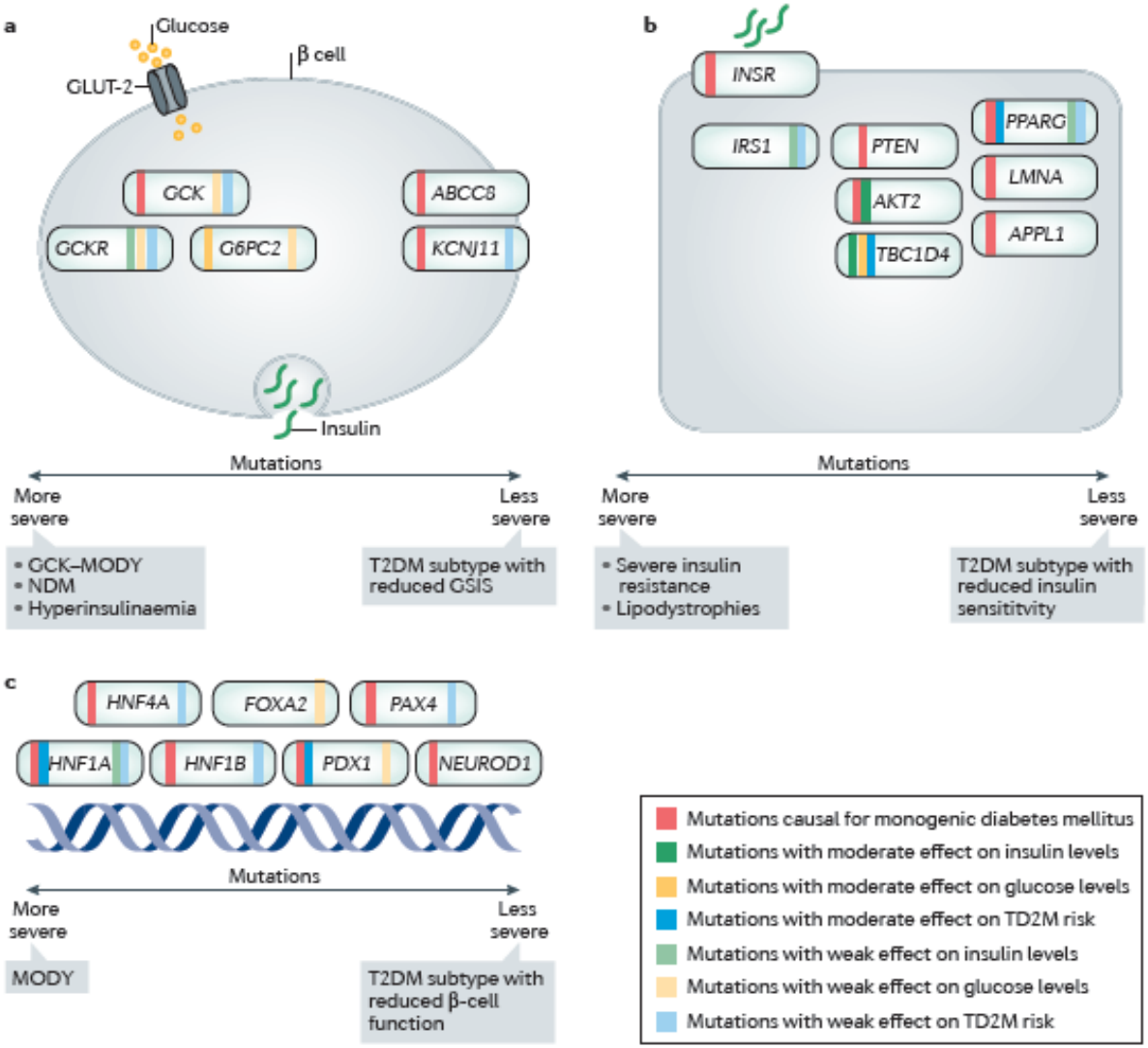

*1 patient had a dual diagnosis of HNF4A and Type 1

# Common and rare forms of diabetes mellitus: towards a continuum of diabetes subtypes




**Monogenic forms of diabetes mellitus**

# A unified model of diabetes mellitus risk.



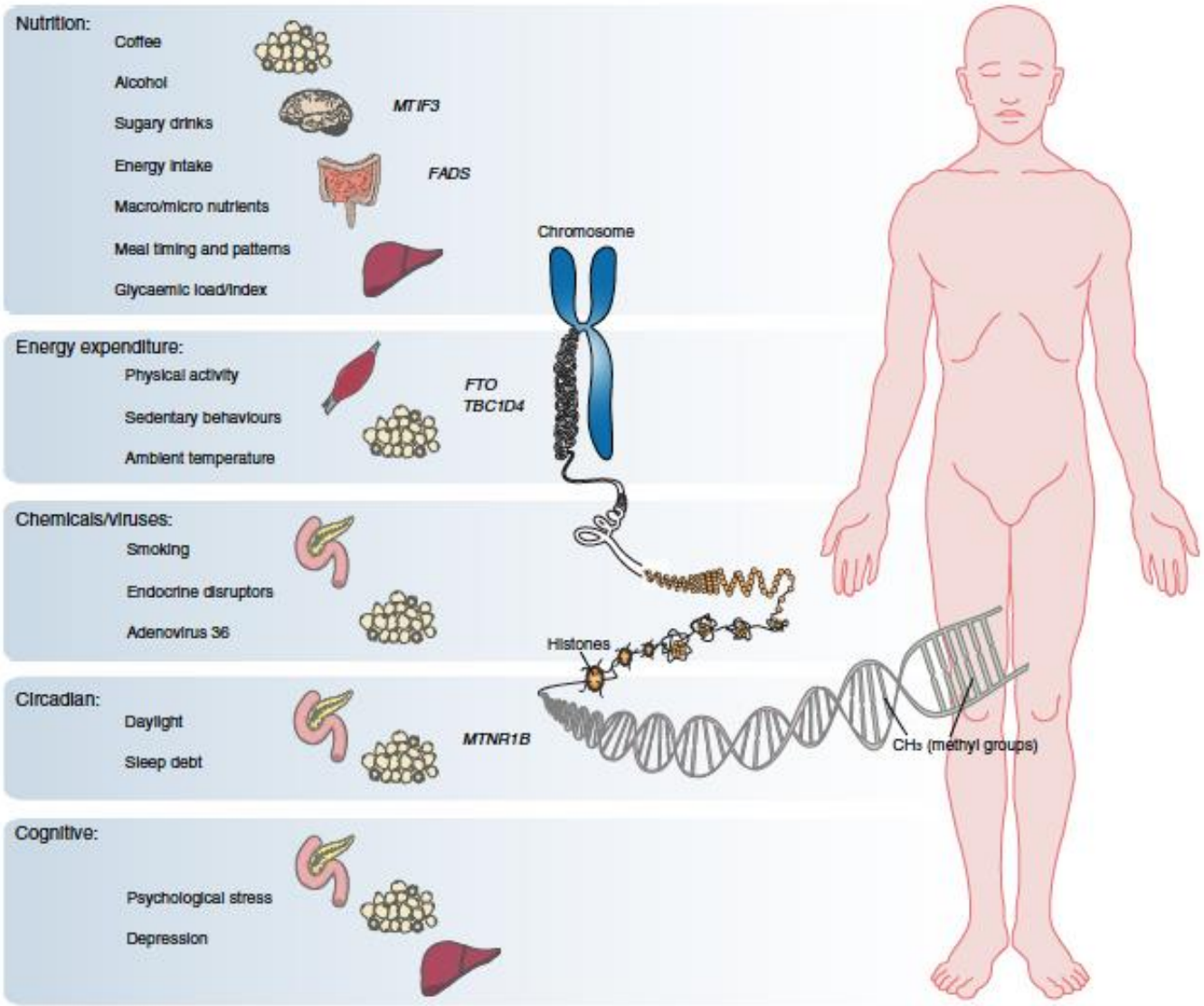

NATURE REVIEWS | ENDOCRINOLOGY

# Precision Medicine per la diagnosi di Diabete tipo 2

Toward Precision Medicine:
*TBC1D4* Disruption Is Common
Among the Inuit and Leads to
Underdiagnosis of Type 2 Diabetes


**Diab. Care, 2016 - DOI: 10.2337/dc16-0769**

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




Diabetologia (2017) 60:784–792

# Personalized Nutrition by Prediction of Glycemic Responses

David Zeevi,[1,2,8] Tal Korem,[1,2,8] Niv Zmora,[3,4,5,8] David Israeli,[6,8] Daphna Rothschild,[1,2] Adina Weinberger,[1,2] Orly Ben-Yacov,[1,2] Dar Lador,[1,2] Tali Avnit-Sagi,[1,2] Maya Lotan-Pompan,[1,2] Jotham Suez,[3] Jemal Ali Mahdi,[3] Elad Matot,[1,2] Gal Malka,[1,2] Noa Kosower,[1,2] Michal Rein,[1,2] Gili Zilberman-Schapira,[3] Lenka Dohnalová,[3] Meirav Pevsner-Fischer,[3] Rony Bikovsky,[1,2] Zamir Halpern,[5,7] Eran Elinav,[3,9,*] and Eran Segal[1,2,9,*]

Cell *163*, 1079–1094, November 19, 2015

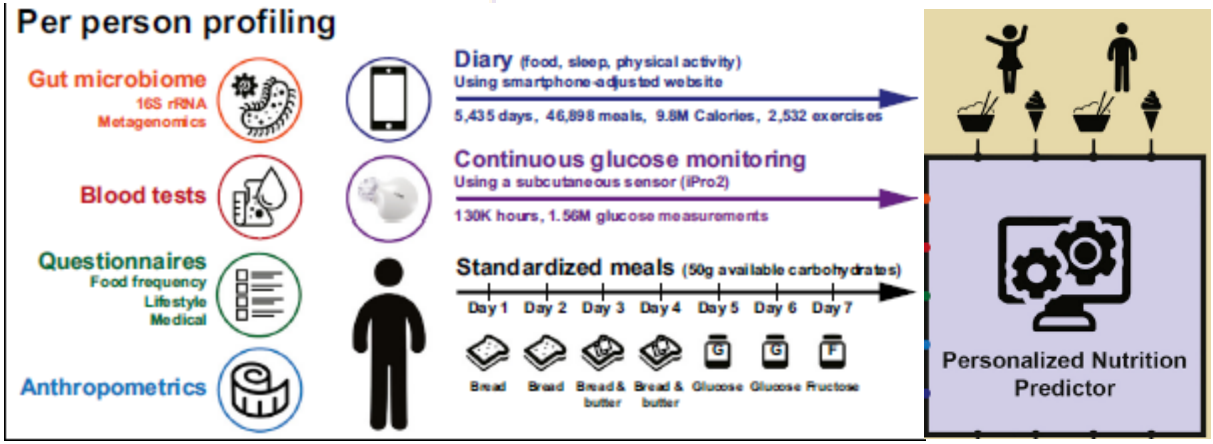
## BACKGROUND

**Elevated postprandial blood glucose levels constitute a global epidemic and a major risk factor for prediabetes and type 2 diabetes, but existing dietary methods for controlling them have limited efficacy.**

***AIM = to quantitatively measure individualized PPGRs, characterize their variability across people, and identify factors associated with this variability.***

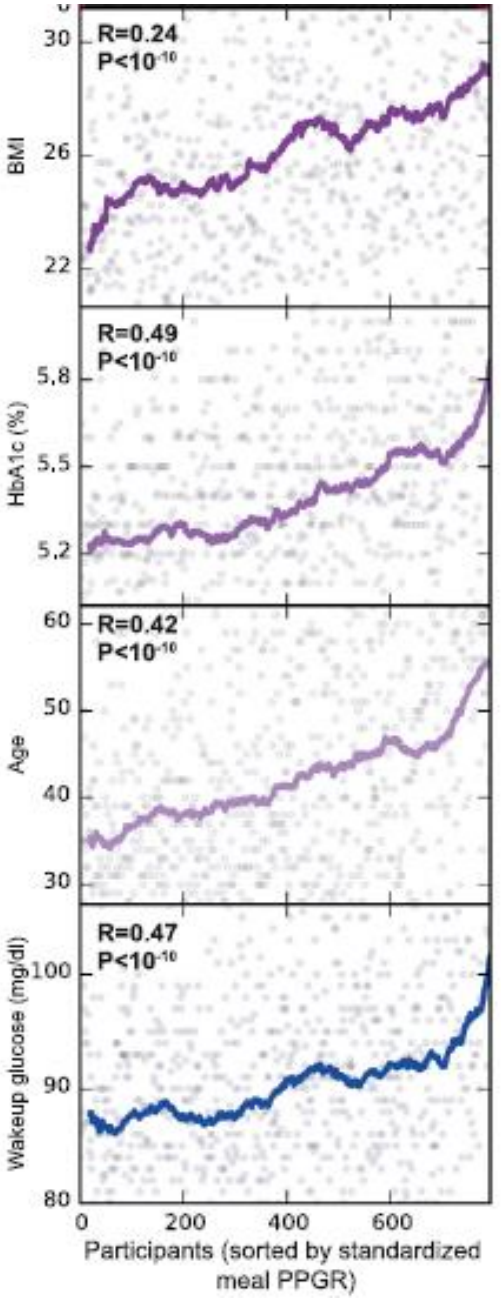
***Starting from these data, the authors devised a machine learning algorithm that accurately predicts personalized PPGRs and used it to develop personally tailored dietary intervention.***

# Measurements of Postprandial Responses, Clinical Data, and Gut Microbiome

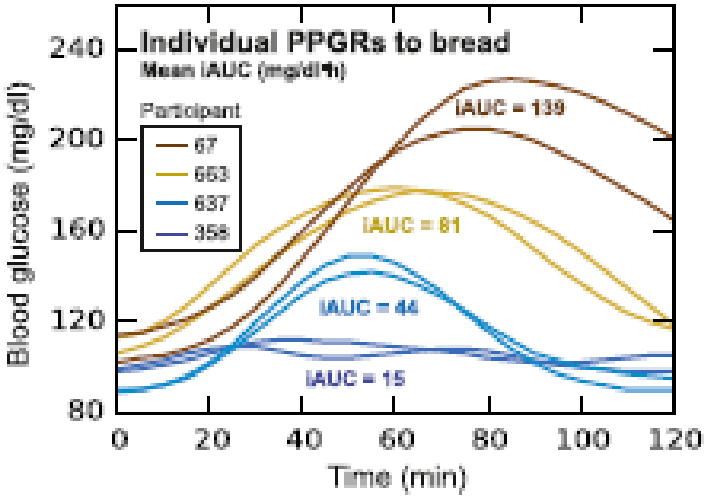


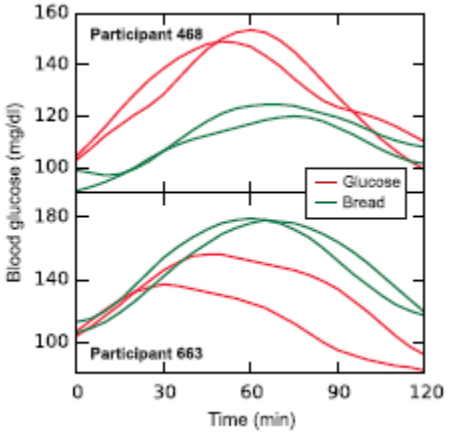

| | Main Cohort |
|---|---|
| Number of participants (n) | 800 |
| Sex (% female) | 60% |
| Age (y) Mean ± SD | 43.3 ± 13.1 |
| BMI (kg/m^2) Mean ± SD | 26.4 ± 5.1 |
| BMI ≥ 25 | 428 (54%) |
| BMI ≥ 30 | 173 (22%) |
| HbA1c% Mean ± SD | 5.43 ± 0.45 |
| HbA1c% ≥ 5.7 | 189 (24%) |
| HbA1c% ≥ 6.5 | 23 (3%) |
| Total cholesterol (non-fasting, mg/dl) Mean ± SD | 186.8 ± 37.5 |
| HDL cholesterol (non-fasting, mg/dl) Mean ± SD | 59.0 ± 17.8 |
| Waist-to-hip circumference ratio Mean ± SD | 0.83 ± 0.12 |

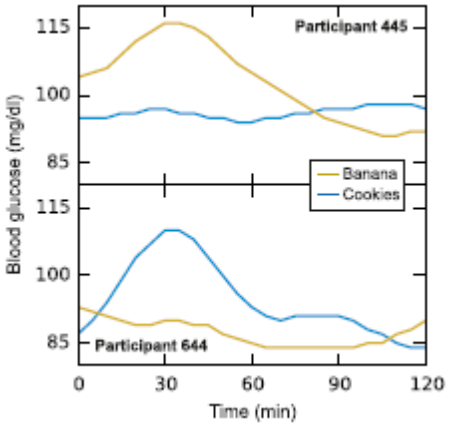
PPGR to standardized meals was significantly correlated with known risk factors



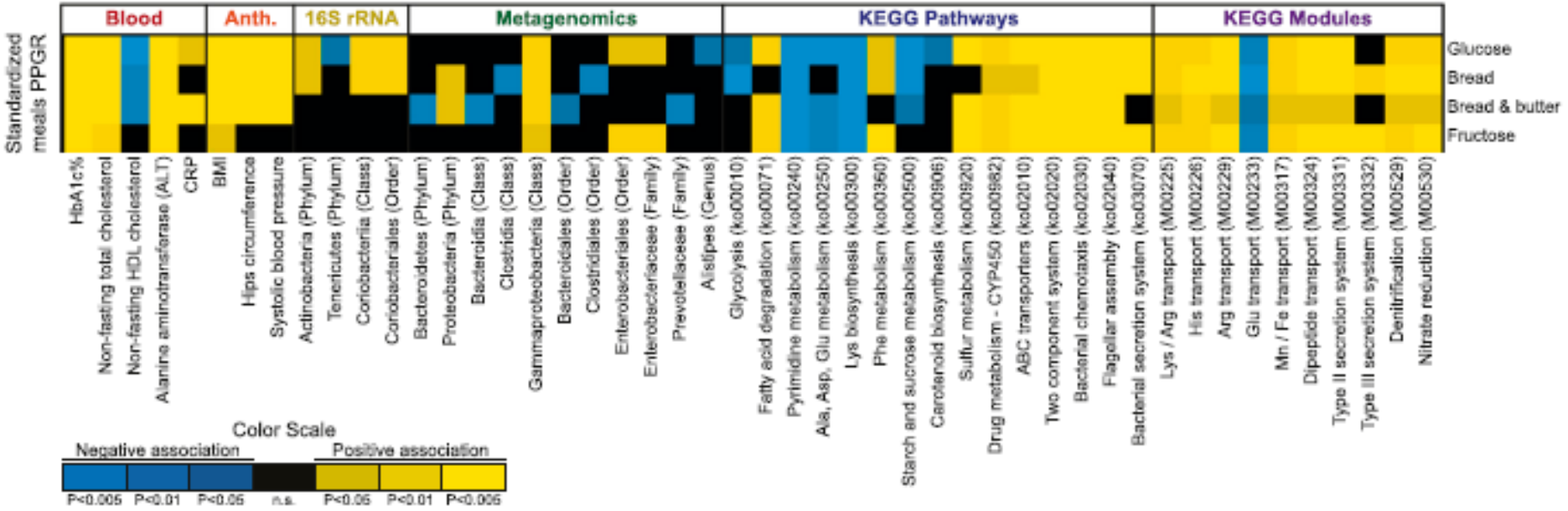
# Individual PPGR to identical meals is reproducible within the same person, but shows a high interpersonal variability



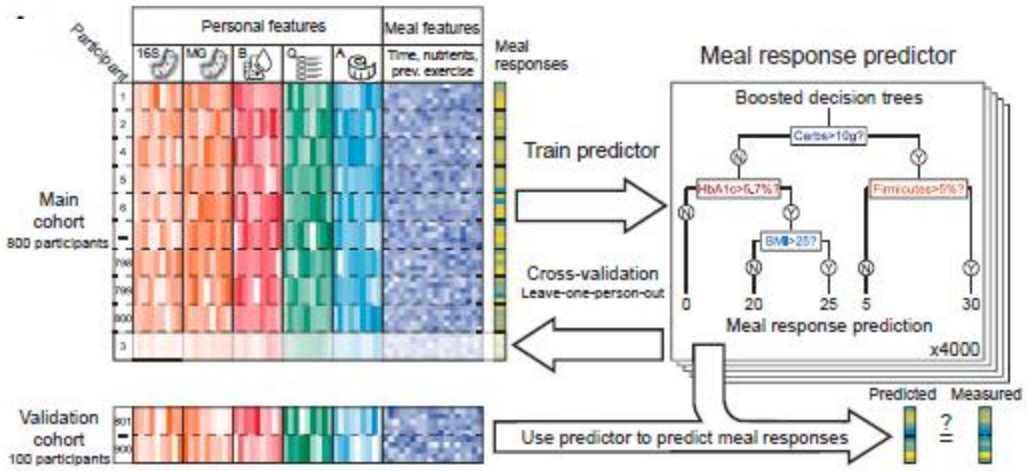



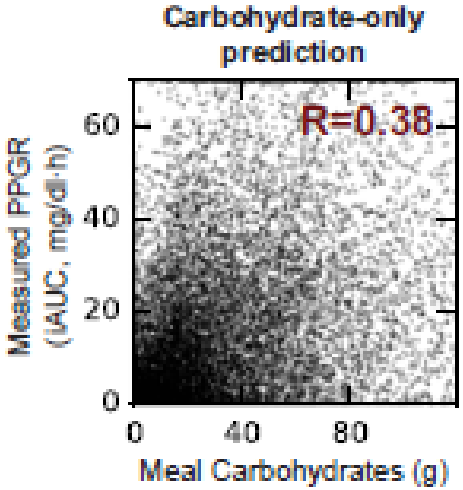

# Multiple significant association were found between the standardized meal PPGRs of participants and both their clinical and gut microbiome data

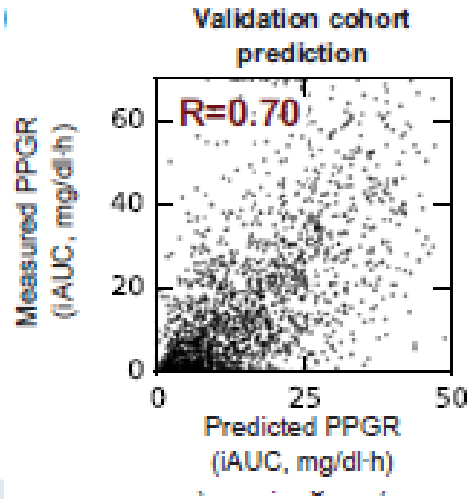


Authors developed an algorithm on the main cohort, which integrates clinical and biochemical data, based on gradient-boosting regression




Compared to the reference model, the algorithm shows a higher correlation with PPGRs – both in the main and in the validation cohort




The algorithm was validated on an independent cohort of 100 participants (PPGRs was predicted using the model trained on the main cohort)
As baseline reference, CHO counting model was used (current gold standard)

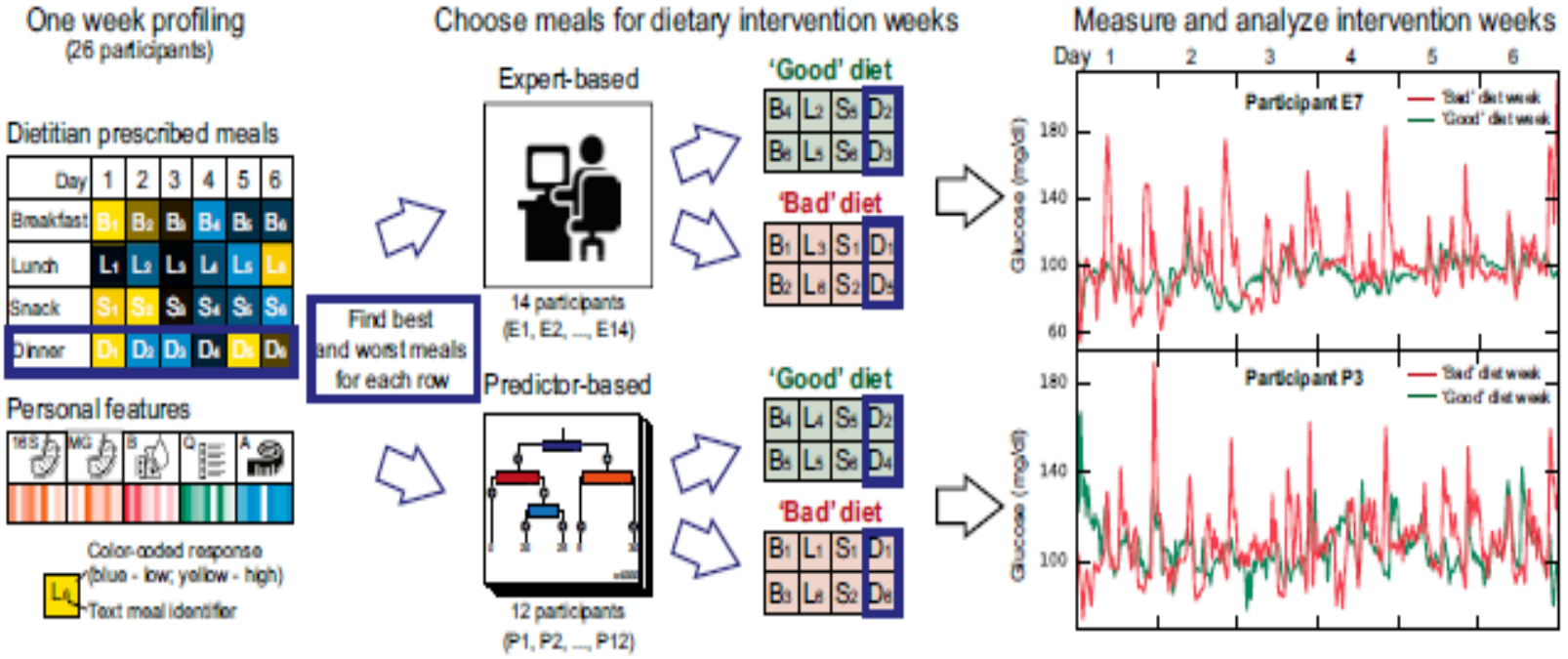
| | Validation Cohort | KS p Value |
|---|---|---|
| Number of participants (n) | 100 | |
| Sex (% female) | 60% | 1 |
| Age (y) Mean ± SD | 42.4 ± 12.6 | 0.972 |
| BMI (kg/m^2) Mean ± SD | 26.5 ± 4.8 | 0.867 |
| BMI ≥ 25 | 50 (50%) | |
| BMI ≥ 30 | 18 (18%) | |
| HbA1c% Mean ± SD | 5.50 ± 0.55 | 0.492 |
| HbA1c% ≥ 5.7 | 31 (31%) | |
| HbA1c% ≥ 6.5 | 3 (3%) | |
| Total cholesterol (non-fasting, mg/dl) Mean ± SD | 182.7 ± 35.7 | 0.231 |
| HDL cholesterol (non-fasting, mg/dl) Mean ± SD | 55.0 ± 16.1 | 0.371 |
| Waist-to-hip circumference ratio Mean ± SD | 0.84 ± 0.07 | 0.818 |

KS = Kolmogorov-Smirnov test versus Main Cohort

# Personally Tailored Dietary Interventions Improve Postprandial Responses

**Could personally tailored dietary interventions based on the prediction algorithm improve PPGRs?**

26 new participants → two-arm blinded randomized controlled trial



# The Impact of Precision Medicine in Diabetes: A Multidimensional Perspective

*Stephen S. Rich[1] and William T. Cefalu[2]*

*Diabetes Care 2016;39:1854–1857 | DOI: 10.2337/dc16-1833*

## Farmacogenomica e risposta alle sulfoniluree

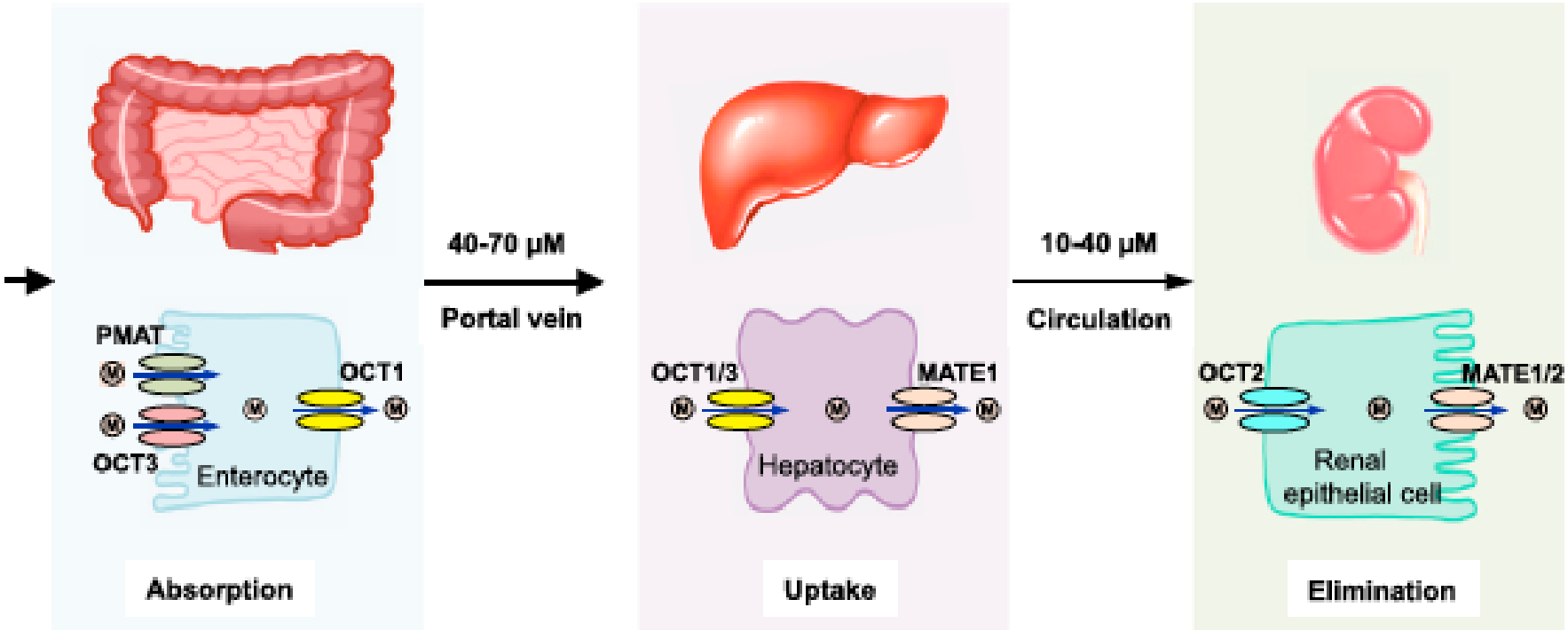
**Table 2—Selected pharmacogenomic findings for sulfonylureas and metformin**

| Drug | Locus | Phenotype | *N* | Effect** | Refs. |
|---|---|---|---|---|---|
| Sulfonylureas | | | | | |
| Pharmacokinetic | *CYP2C9* | $HbA_{1c}$ response | 1,073 | 0.5% absolute greater reduction in $HbA_{1c}$ (homozygous for variant alleles) | 64 |
| | | FBG response | 475 | No association | 75 |
| | | Hypoglycemia | 357 | OR 5.2 for hypoglycemia (homozygous for variant alleles) | 65 |
| Pharmacodynamic | *KCNJ11/ABCC8** | $HbA_{1c}$ and FBG response | 1,268 | 3.5% relative greater reduction in $HbA_{1c}$ and 7.7% relative greater reduction in FBG (homozygous for variant alleles) | 66 |
| | | $HbA_{1c}$ response | 101 | 0.2% absolute greater reduction in $HbA_{1c}$ (per variant allele) | 67 |
| | | Insulin treatment | 525 | No association | 68 |
| | | FBG response | 228 | No association | 69 |
| | | $HbA_{1c}$ response | 97 | Less reduction in $HbA_{1c}$ | 70 |
| | *TCF7L2* | On treatment $HbA_{1c}$ <7% | 901 | OR 1.9 for treatment failure (homozygous for variant allele) | 164 |
| | | On treatment $HbA_{1c}$ <7% | 189 | OR 1.6 for treatment failure (per variant allele) | 165 |

# Farmacogenomica e risposta alla metformina

| | | | | | |
|---|---|---|---|---|---|
| Metformin | | | | | |
| Pharmacokinetic | *SLC22A1* | $HbA_{1c}$ response | 102 | 0.3% absolute lower reduction in $HbA_{1c}$ (per variant allele) | 166 |
| | | $HbA_{1c}$ response | 371 | 1.1% absolute lower reduction in $HbA_{1c}$ (per variant allele) | 77 |
| | | On treatment $HbA_{1c}$ <7% | 1,531 | No association | 76 |
| | | Drug intolerance | 2,166 | OR 2.4 for discontinuation (homozygous for variant alleles) | 73 |
| | *SLC47A1* | $HbA_{1c}$ response | 116 | 0.3% absolute lower reduction in $HbA_{1c}$ (per variant allele) | 167 |
| | | $HbA_{1c}$ response | 371 | No association | 77 |
| | | Risk of type 2 diabetes | 2,994 | Less reduction in diabetes risk | |
| | *SLC47A2* | $HbA_{1c}$ response | 253 | 0.1% absolute lower reduction in $HbA_{1c}$ (any variant allele) | 168 |
| | | $HbA_{1c}$ response | 371 | No association | 77 |
| GWA studies | *ATM* | $HbA_{1c}$ response, on treatment $HbA_{1c}$ <7% | 2,896 | 0.1% absolute greater reduction in $HbA_{1c}$ and OR 1.4 for treatment success (per variant allele) | 80 |
| | | $HbA_{1c}$ response, on treatment $HbA_{1c}$ <7% | 1,366 | No association with $HbA_{1c}$ response, OR 1.2 for treatment success (per variant allele) | 81 |

# Metformin Action: Concentrations Matter

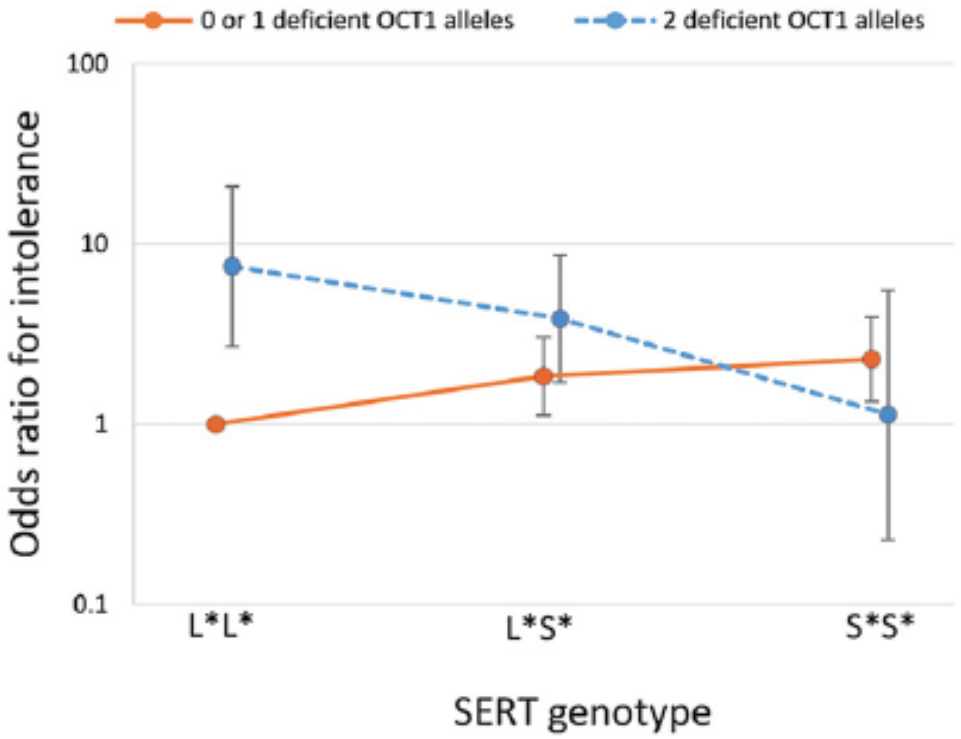



Cell Metabolism 21, February 3, 2015

# Effect of Serotonin Transporter 5-HTTLPR Polymorphism on Gastrointestinal Intolerance to Metformin: A GoDARTS Study

*Tanja Dujic,[1,2] Kaixin Zhou,[2] Roger Tavendale,[2] Colin N.A. Palmer,[2] and Ewan R. Pearson[2]*

*DOI: 10.2337/dc16-0706*

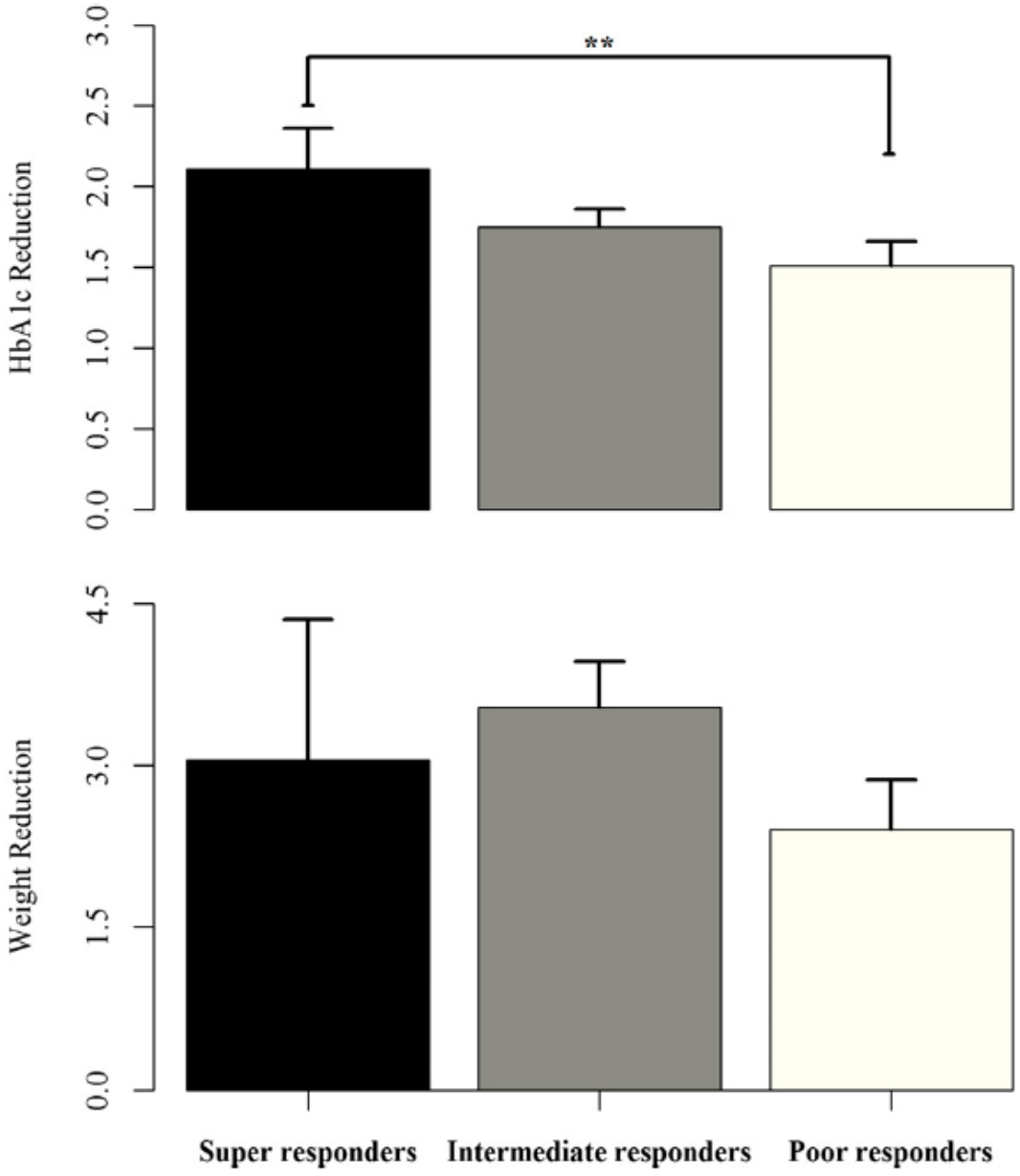



Numbers of intolerant/tolerant individuals

| | SERT genotype | | |
|---|---|---|---|
| OCT1 genotype | L*L* | L*S* | S*S* |
| 0 or 1 deficient OCT1 allele | 26/362 | 68/605 | 47/298 |
| 2 deficient OCT1 alleles | 8/20 | 13/51 | 2/20 |

# CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes

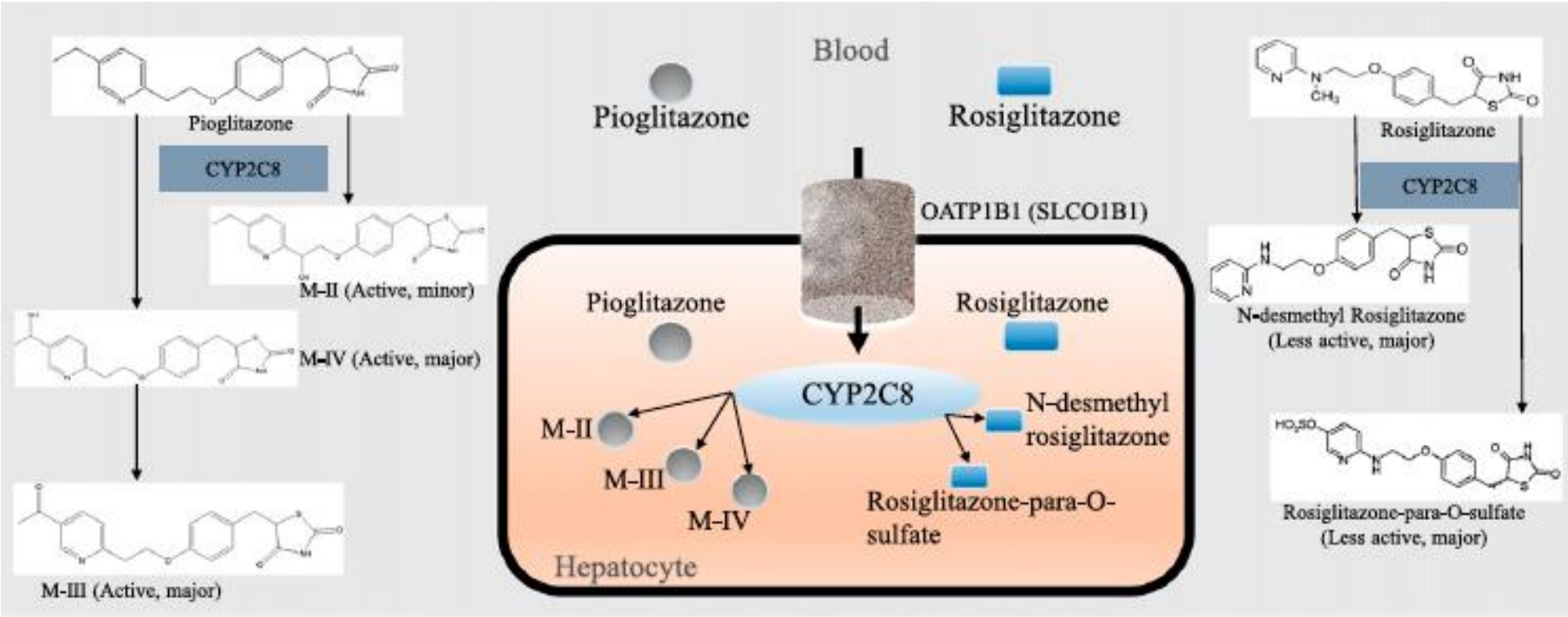
**Diabetes Care**



# CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes

*Adem Y. Dawed, Louise Donnelly, Roger Tavendale, Fiona Carr, Graham Leese, Colin N.A. Palmer, Ewan R. Pearson, and Kaixin Zhou*

*DOI: 10.2337/dc15-2464*

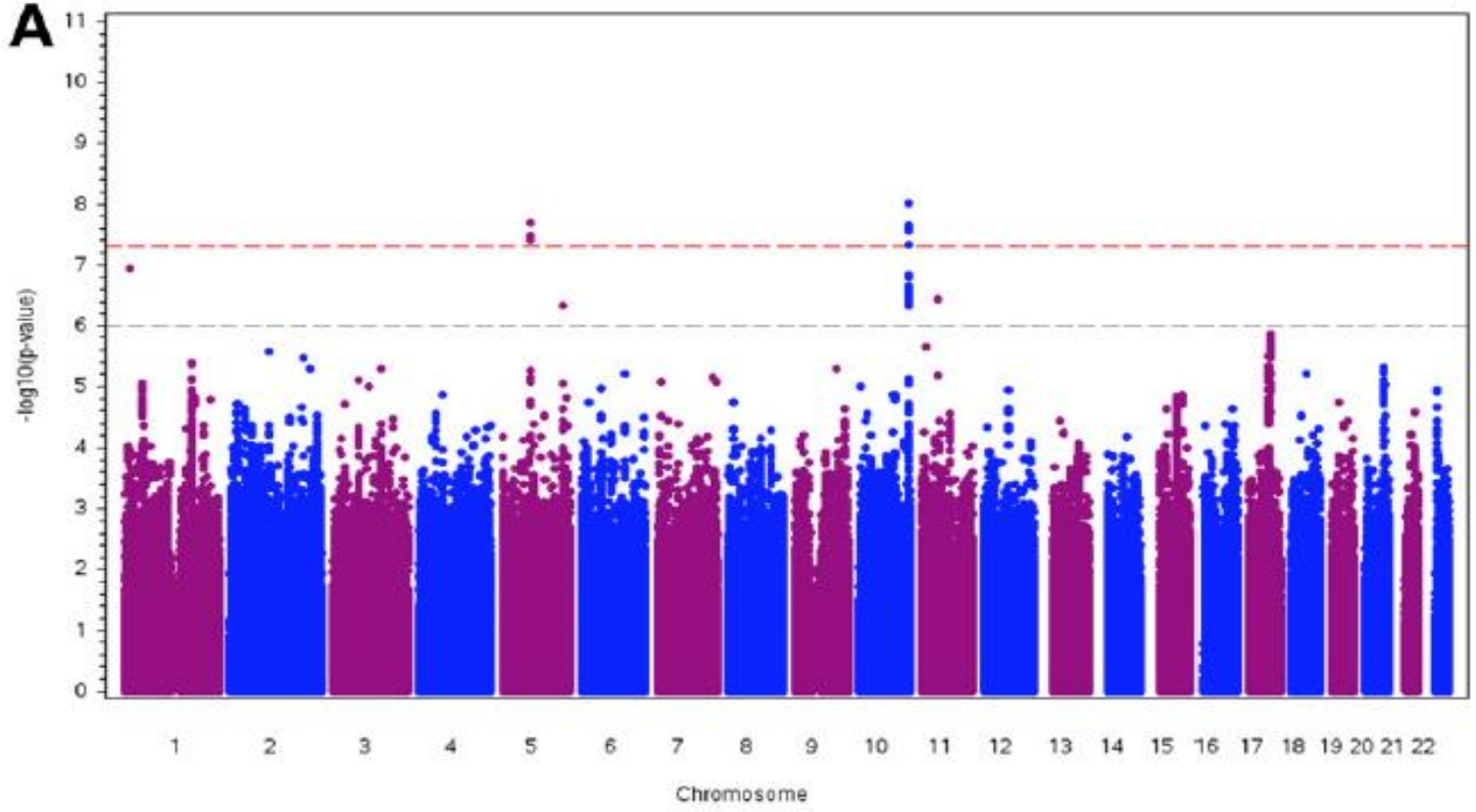


# Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Control in Type 2 Diabetes: Findings From the ACCORD Clinical Trial

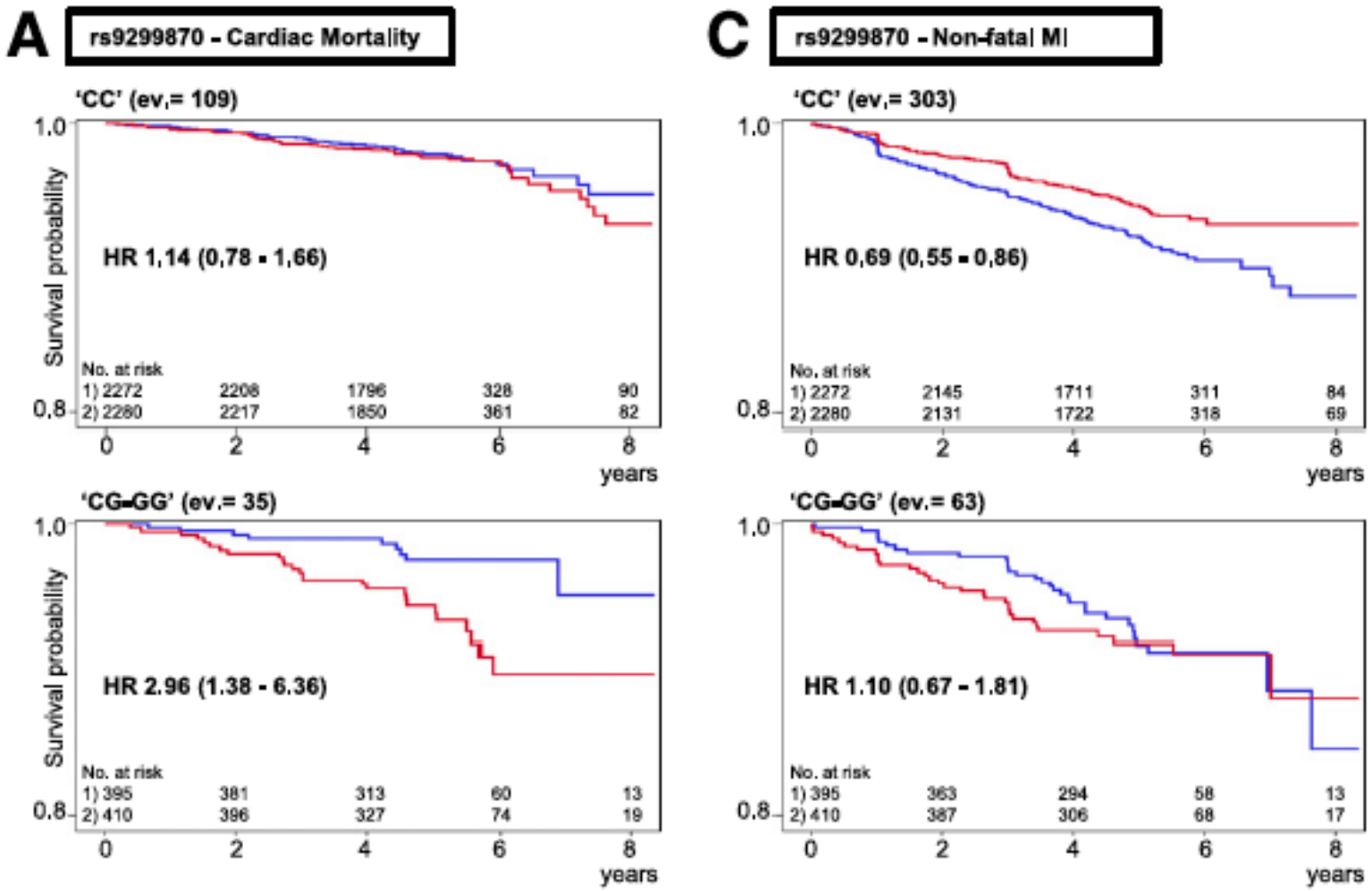
DOI: 10.2337/dc16-0285

Hetal S. Shah,[1,2] He Gao,[1,2] Mario Luca Morieri,[1,2] Jan Skupien,[1,2,3] Skylar Marvel,[4] Guillaume Paré,[5] Gaia C. Mannino,[1,2] Patinut Buranasupkajorn,[1,2,6] Christine Mendonca,[1] Timothy Hastings,[1] Santica M. Marcovina,[7] Ronald J. Sigal,[8] Hertzel C. Gerstein,[5] Michael J. Wagner,[9] Alison A. Motsinger-Reif,[4] John B. Buse,[10] Peter Kraft,[11] Josyf C. Mychaleckyj,[12] and Alessandro Doria[1,2]

**Two genetic loci, at 10q26 and 5q13, predict the cardiovascular effects of intensive glycemic control in ACCORD.**

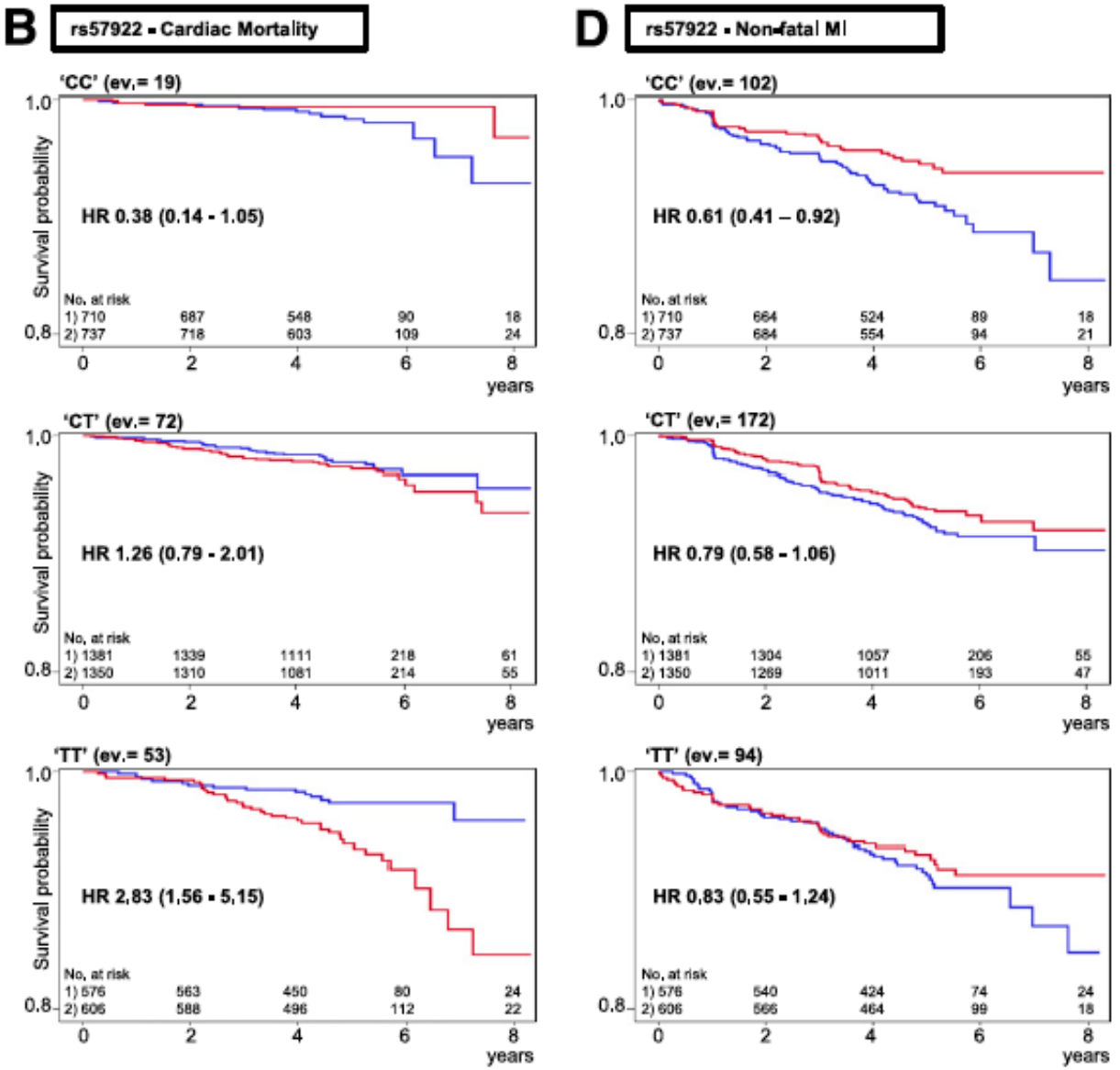


# Two genetic loci, at 10q26 and 5q13, predict the cardiovascular effects of intensive glycemic control in ACCORD.




**MGMT functions as a negative regulator of ESR1 (estrogen receptor 1)**

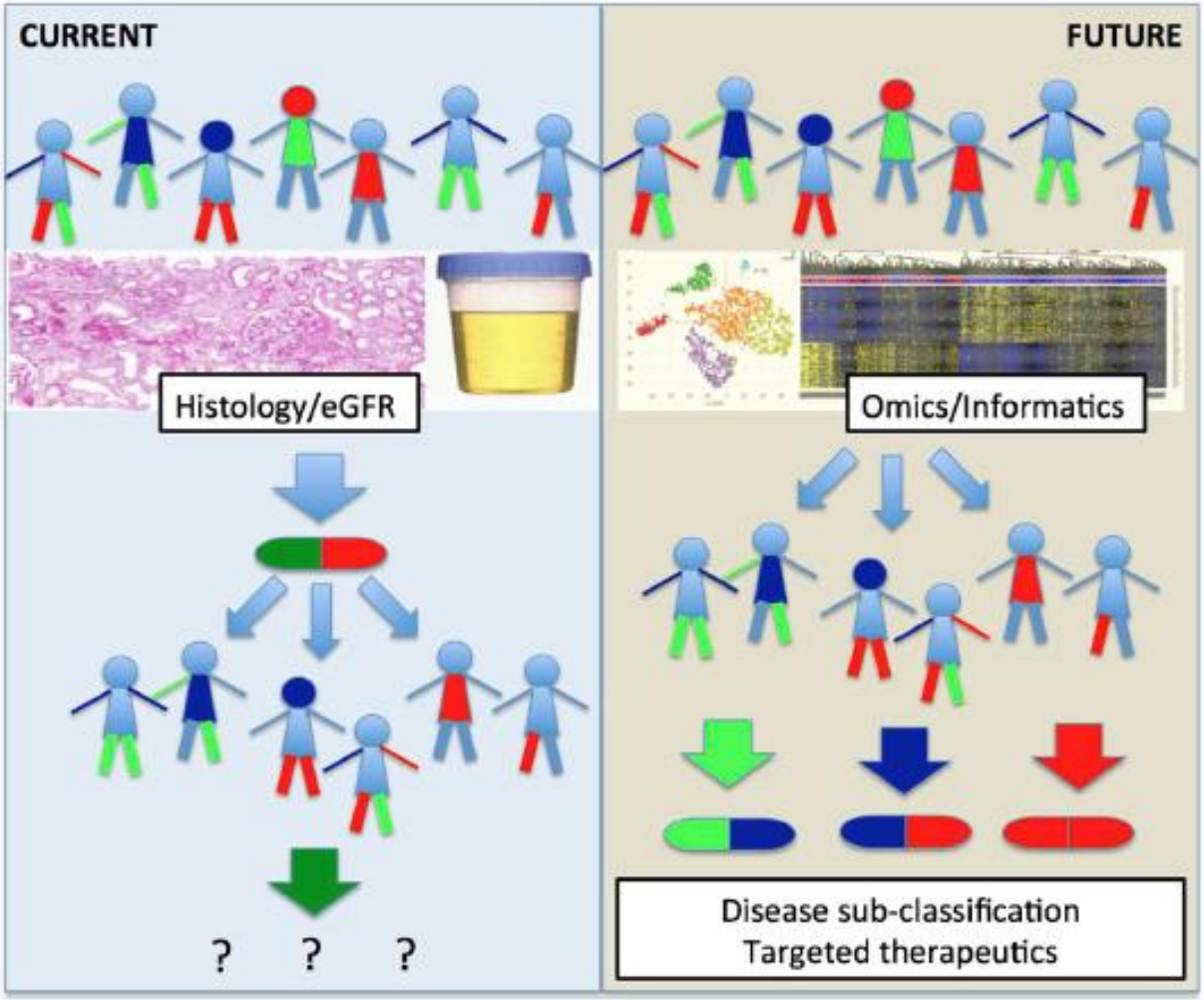
# Two genetic loci, at 10q26 and 5q13, predict the cardiovascular effects of intensive glycemic control in ACCORD




**NSA2 is a hyperglycemia-induced gene associated with diabetic nephropathy and involved in the TGF-b1 pathway**

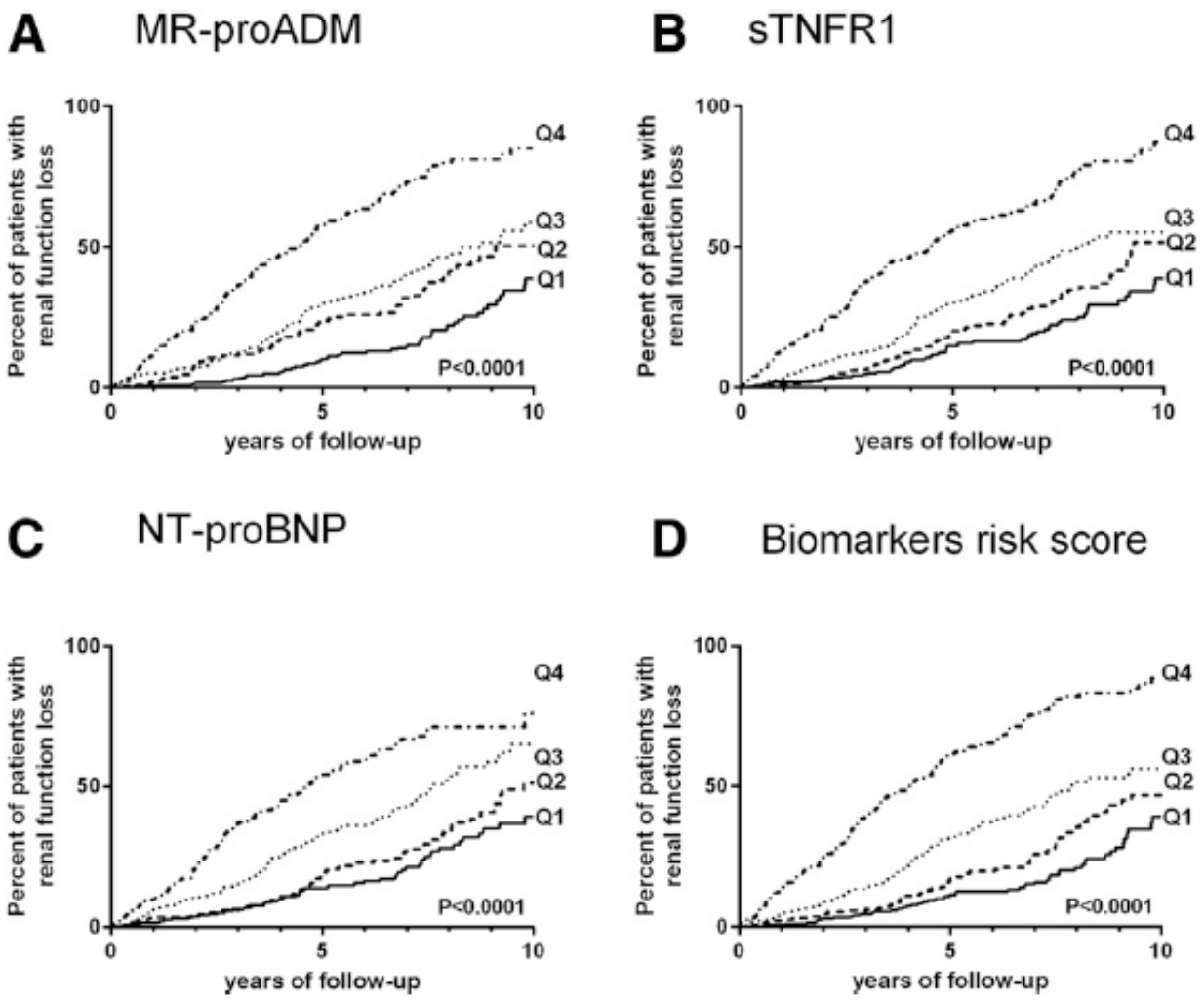
# Precision Medicine Approaches to Diabetic Kidney Disease: Tissue as an Issue

Curr Diab Rep (2017) 17:30



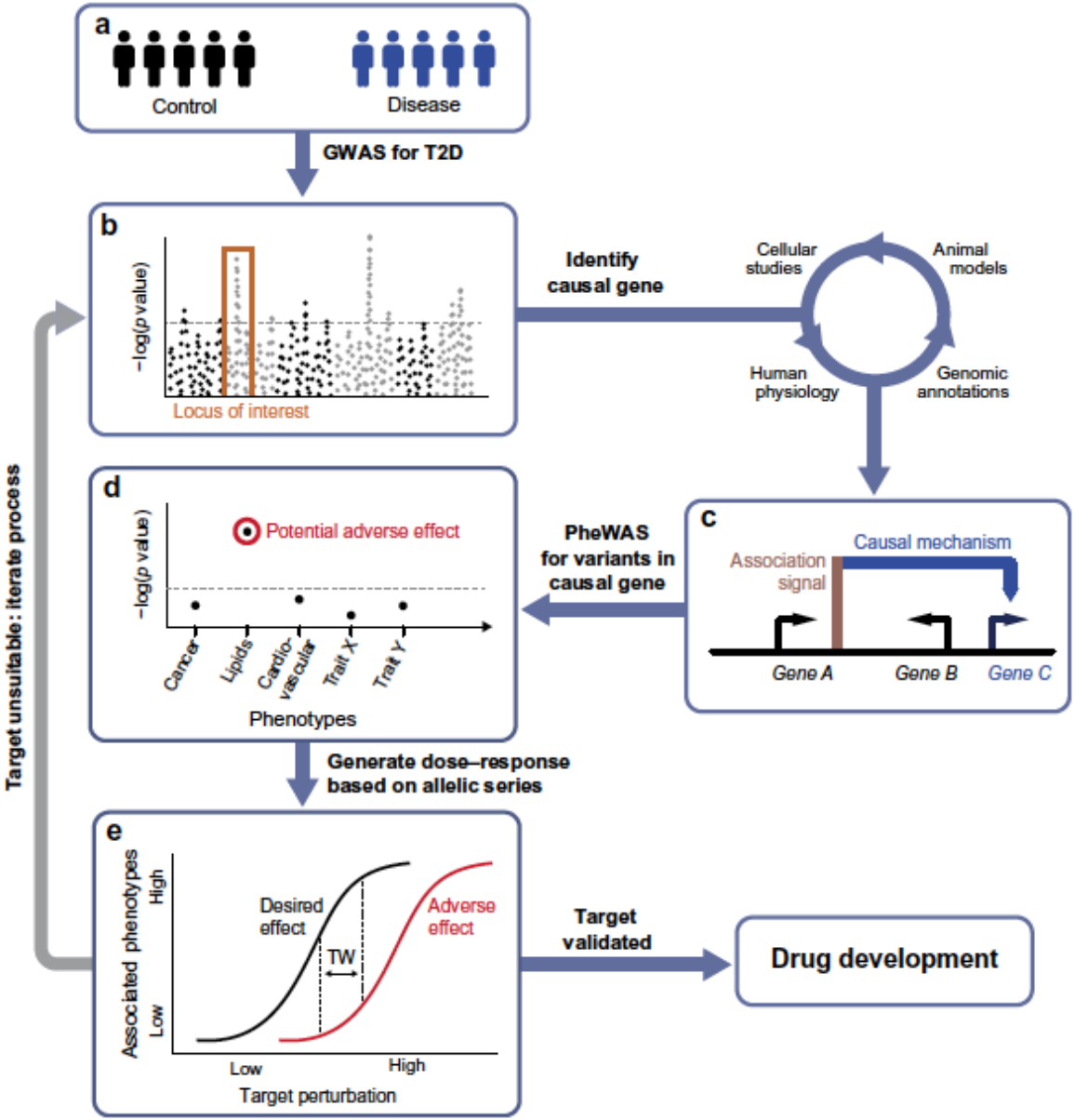
Association of Circulating Biomarkers (Adrenomedullin, TNFR1, and NT-proBNP) With Renal Function Decline in Patients With Type 2 Diabetes: A French Prospective Cohort

**Diabetes Care**



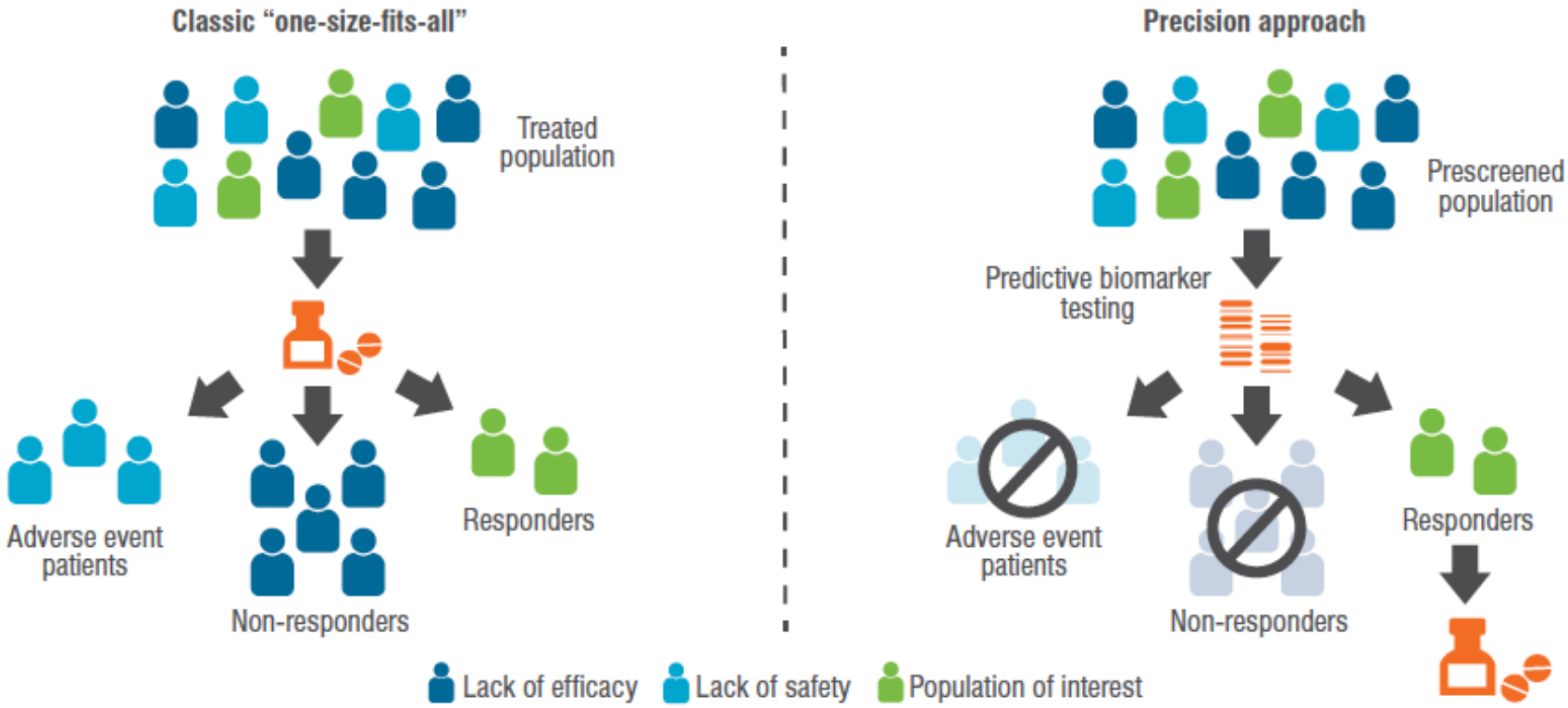
# Human genetics as a model for target validation: finding new therapies for diabetes

Diabetologia (2017) 60:960–970

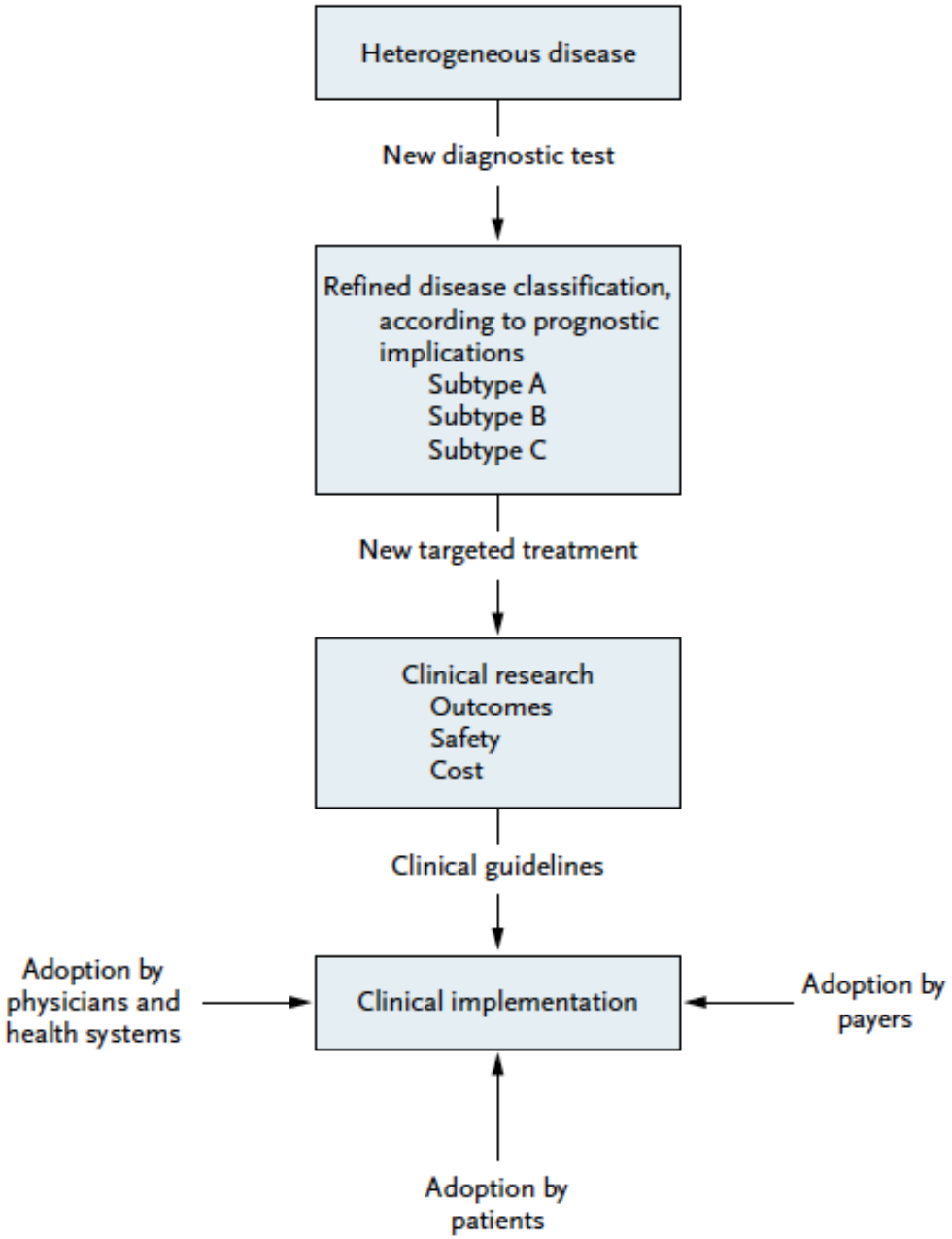


## *Changing how drugs are delivered*

Identify non-responders and safety issues before prescribing or treating



# “Precision” PDTA



# Utilità clinica; implicazioni etiche e legali

| | | |
|---|---|---|
| Clinical utility | What is the impact of a positive or negative test on patient care in terms of health outcomes? | What is the absolute change in $HbA_{1c}$ lowering associated with the *ATM* locus for metformin treatment response? Does this pharmacogenomic test result in projected or tangible health benefits in terms of clinical complications, such as a reduced risk of blindness or cardiovascular disease? |
| | What are the financial costs associated with testing and the economic benefits associated with actions resulting from testing? | What is the cost to test for the common *TCF7L2* variant for type 2 diabetes risk, including laboratory, reporting, educational, and counseling costs? What is the cost per case of diabetes predicted? Does this test result in cost-effective screening or prevention of diabetes later in life? |
| | What educational materials for patients have been developed and validated? | Do educational materials clearly explain the magnitude of the increased risk of type 2 diabetes associated with the common *TCF7L2* variant in relation to other known risk factors? |
| Ethical, legal, and social implications | What is known about how this test could lead to stigmatization, discrimination, privacy/ confidentiality, and personal/family social issues? | Does the identification of a pathogenic variant responsible for a hereditary form of early-onset diabetes have implications for family planning? |
| | Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, disclosure, or reporting requirements? | Are physicians providing sufficient information about the potential risks and benefits from genetic testing so that patients can make informed decisions? |
| | What safeguards have been described and are these safeguards effective? | |

# Precision Medicine: Azioni da intraprendere

Risulta per questo fondamentale il ruolo del decisore politico e del Sistema Sanitario (nazionale e regionale) che, da un lato, investa in un paradigma in grado di trasformare l'approccio e gli strumenti di screening, diagnosi e cura, e dall'altro lato, supporti il cambiamento degli attori di questo ecosistema e, in particolare, si faccia promotore di un'azione di sensibilizzazione verso i pazienti e i volontari sani che, condividendo i dati, possono creare le solide basi su cui fondare la **Precision Medicine**.

In particolare, si dovrà lavorare in parallelo per:

- ✓ Creare una rete nazionale della *Precision Medicine;*
- ✓ Standardizzare la raccolta e la strutturazione dei dati;
- ✓ Realizzare piattaforme specialistiche integrate sul territorio nazionale;

# Conclusioni

- **La Medicina di precisione rappresenta uno dei concetti più innovativi nell'ambito della Salute:**

***Diagnosi precoce; trattamenti più efficaci e con meno effetti collaterali***

- **Un motore potenziale per aiutare la crescita economica**

- **Richiede la collaborazione di tutti gli stakeholders:**

***Clinici, ricercatori, aziende ospedaliere, medici di medicina generale, istituzioni di ricerca, enti regolatori, agenzie pubbliche, società scientifiche, istituzioni politiche, assicurazioni, industria, e, soprattutto, i cittadini.***