Dalla classificazione del diabete alla Medicina di Precisione

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

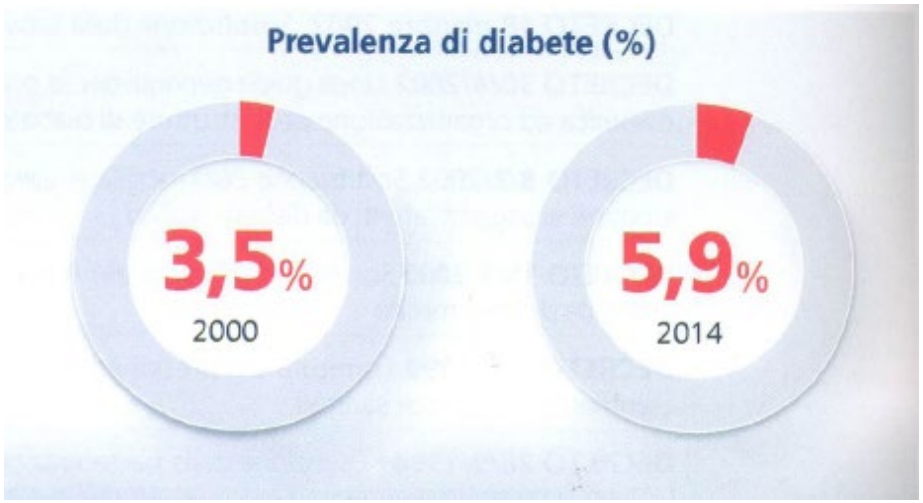
- **Astra Zeneca**
- **Eli Lilly**
- **Novartis**
- **Johnson & Johnson**
- **Merck Sharp & Dohme**
- **Novo Nordisk**

L'impatto del diabete in Toscana

Popolazione 3.750.511 abitanti **Firenze 377.207** abitanti

5,9 cittadini su 100 si dichiarano diabetici in Toscana. La Toscana è una regione con una prevalenza dell'obesità infantile inferiore alla media nazionale, mentre la prevalenza del diabete è superiore alla media a causa di un tasso di crescita della patologia superiore all'andamento nazionale.
Il tasso standardizzato di mortalità per diabete è piuttosto stabile fra il 2000 e il 2011 e resta al di sotto della media nazionale per entrambi i sessi.
I tassi di ospedalizzazione per diabete non controllato, diabete con complicanze ed amputazione risultano nettamente migliori rispetto alla media nazionale.

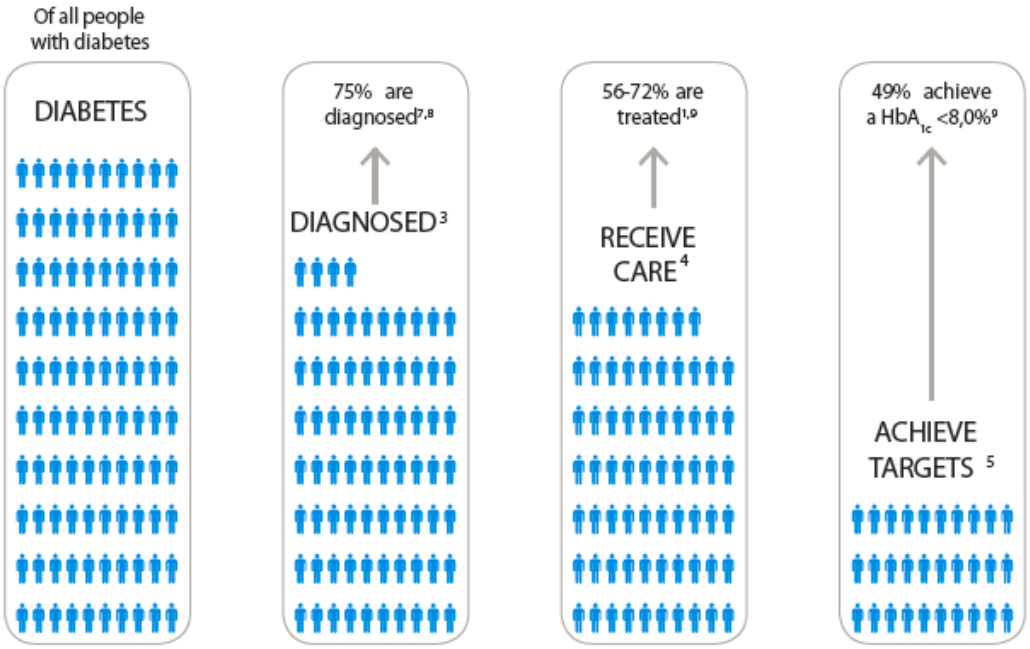
221.000 persone dichiarano di essere diabetiche



Italia

Toscana

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.

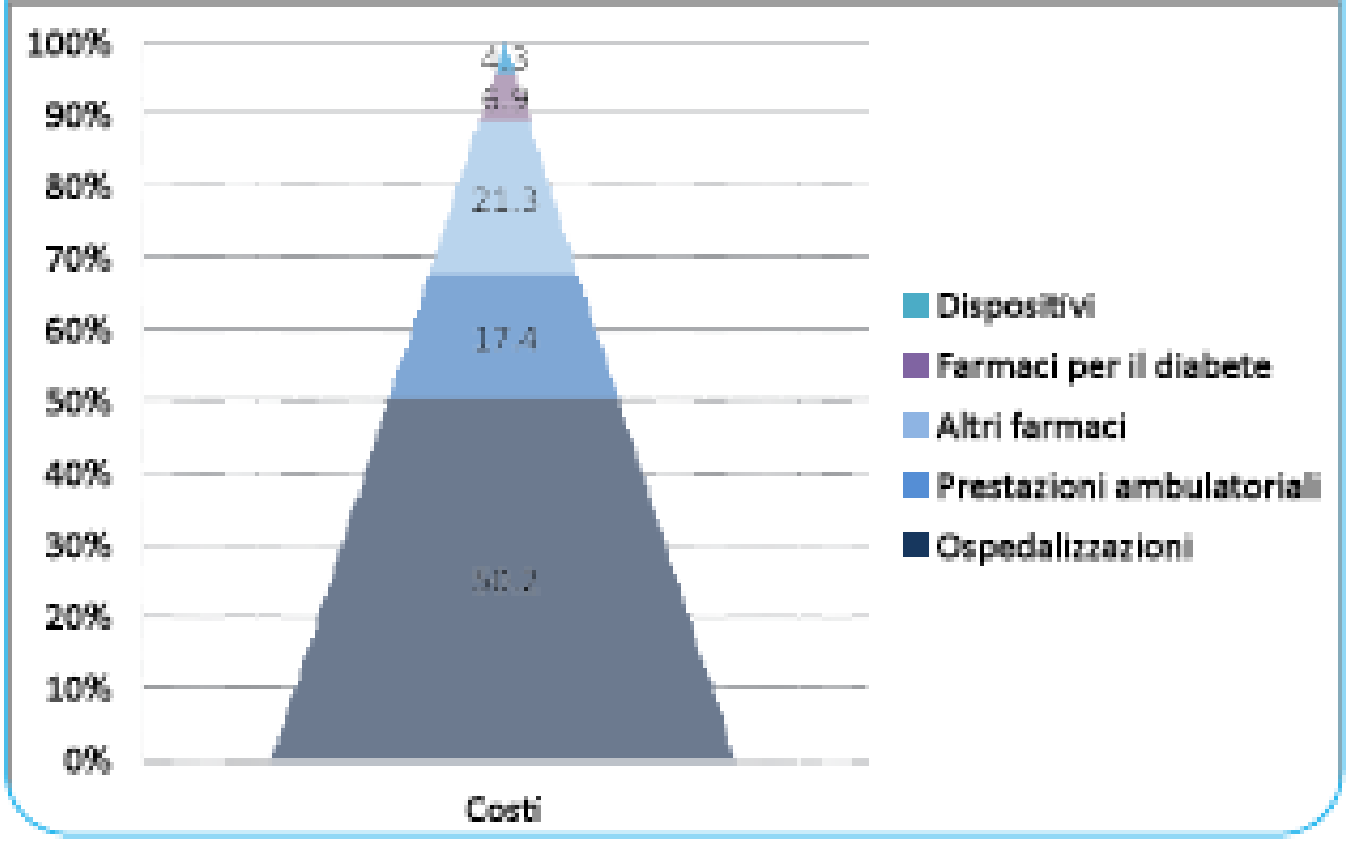
1 VII Report Health Search, Available at: http://healthsearch.it/documenti/Archivio/Report/VIIReport_2011-2012/VII%20Report%20HS.pdf
7 . HealthSearch, data on file.
8- Screening campaign, health district of Siena. Data on file
9. AMD Annals 2011/2012, available at: http://www.infodiabetes.it/files/Annali%202011%20def.pdf

Italian Barometer Diabetes Observatory
Principiis Obsta
Foundation

I costi del diabete

Fattori che contribuiscono ai costi sanitari diretti per il diabete (Osservatorio ARNO 2015)

- ✓Il **10%** della spesa sanitaria in Italia è legata al diabete;
- ✓La maggior parte dei costi del diabete è legato alle ospedalizzazioni.
- ✓I farmaci per il diabete incidono per il **7%**, i presidi per il **4%**.



2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S13–S27 | https://doi.org/10.2337/dc18-S002

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

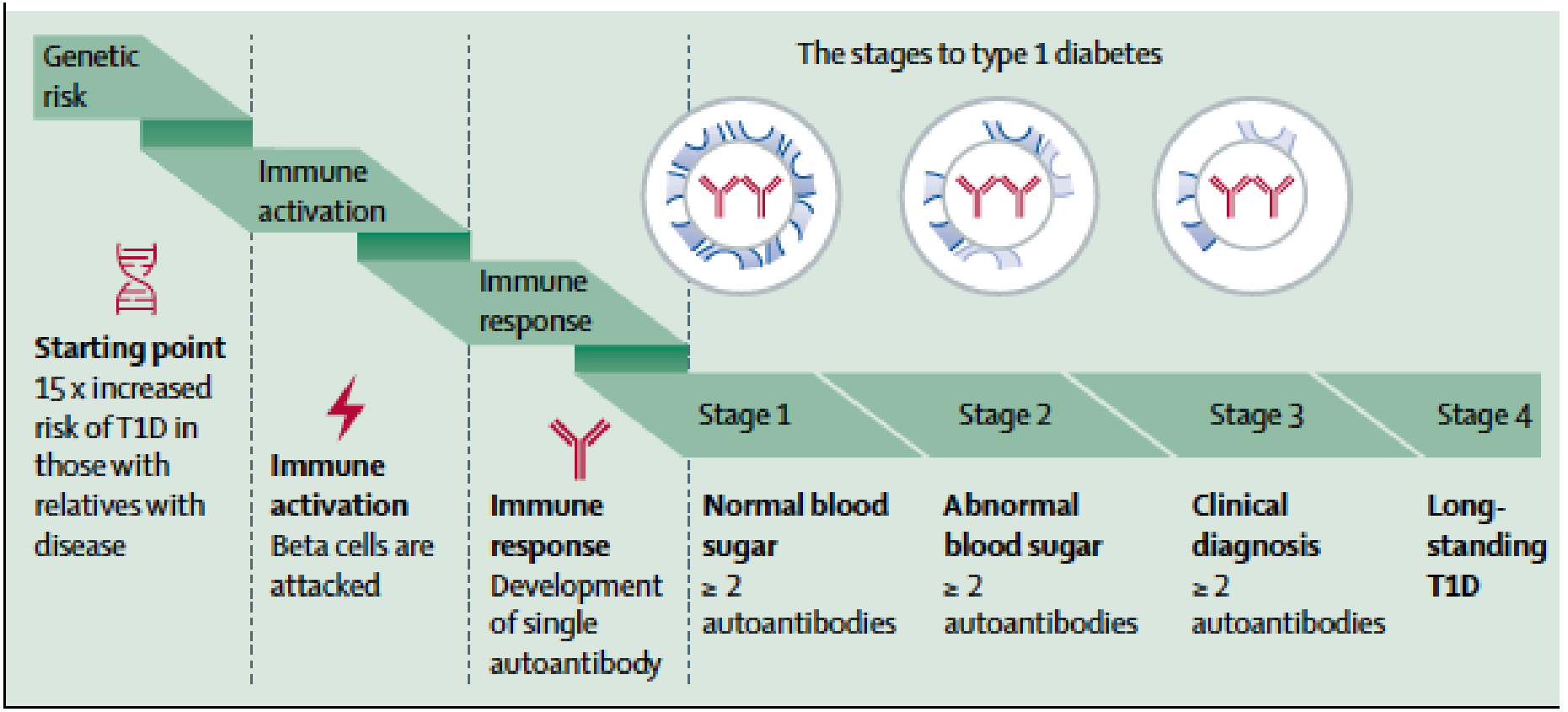
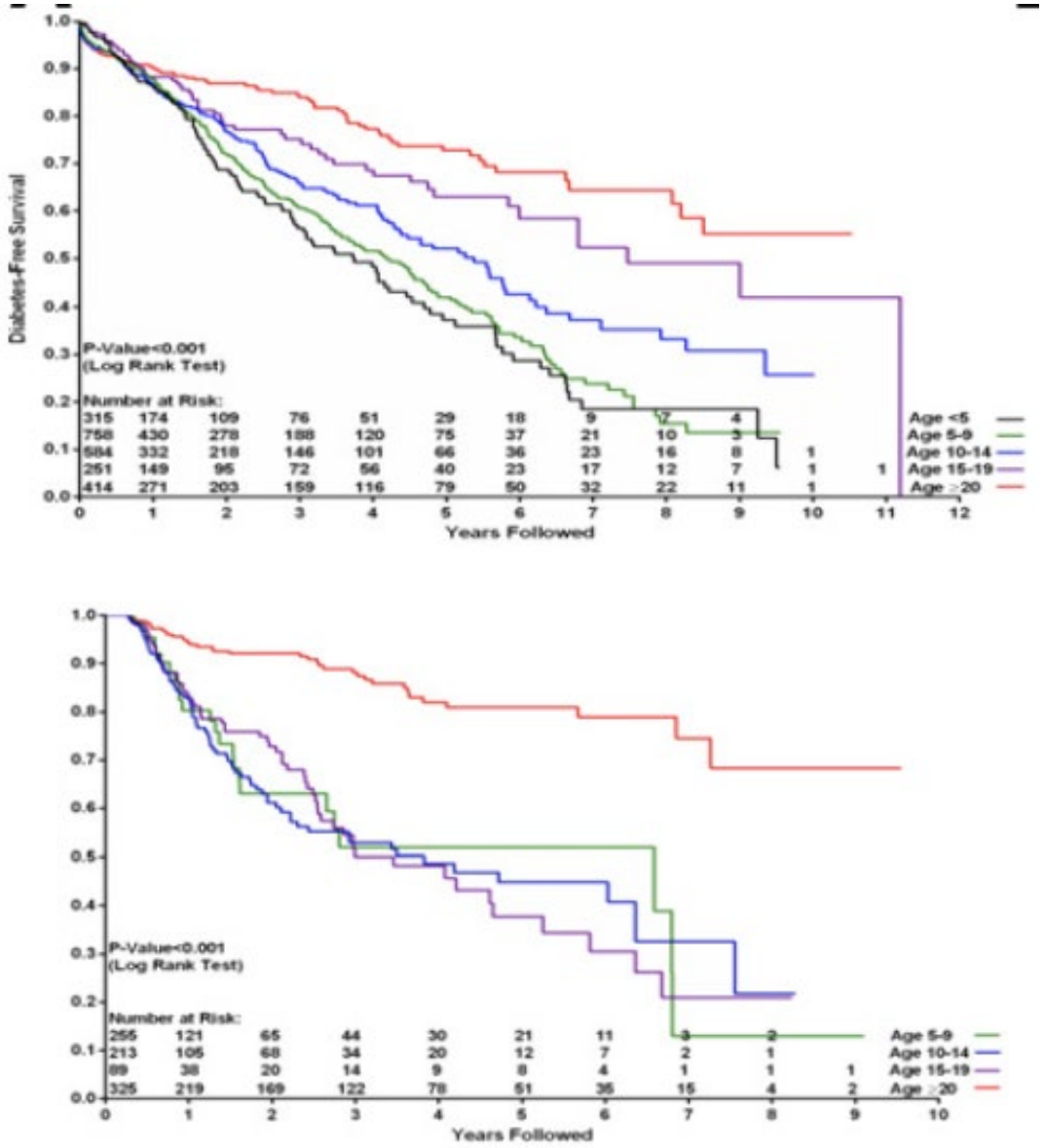


Table 2.1—Staging of type 1 diabetes (4,5)

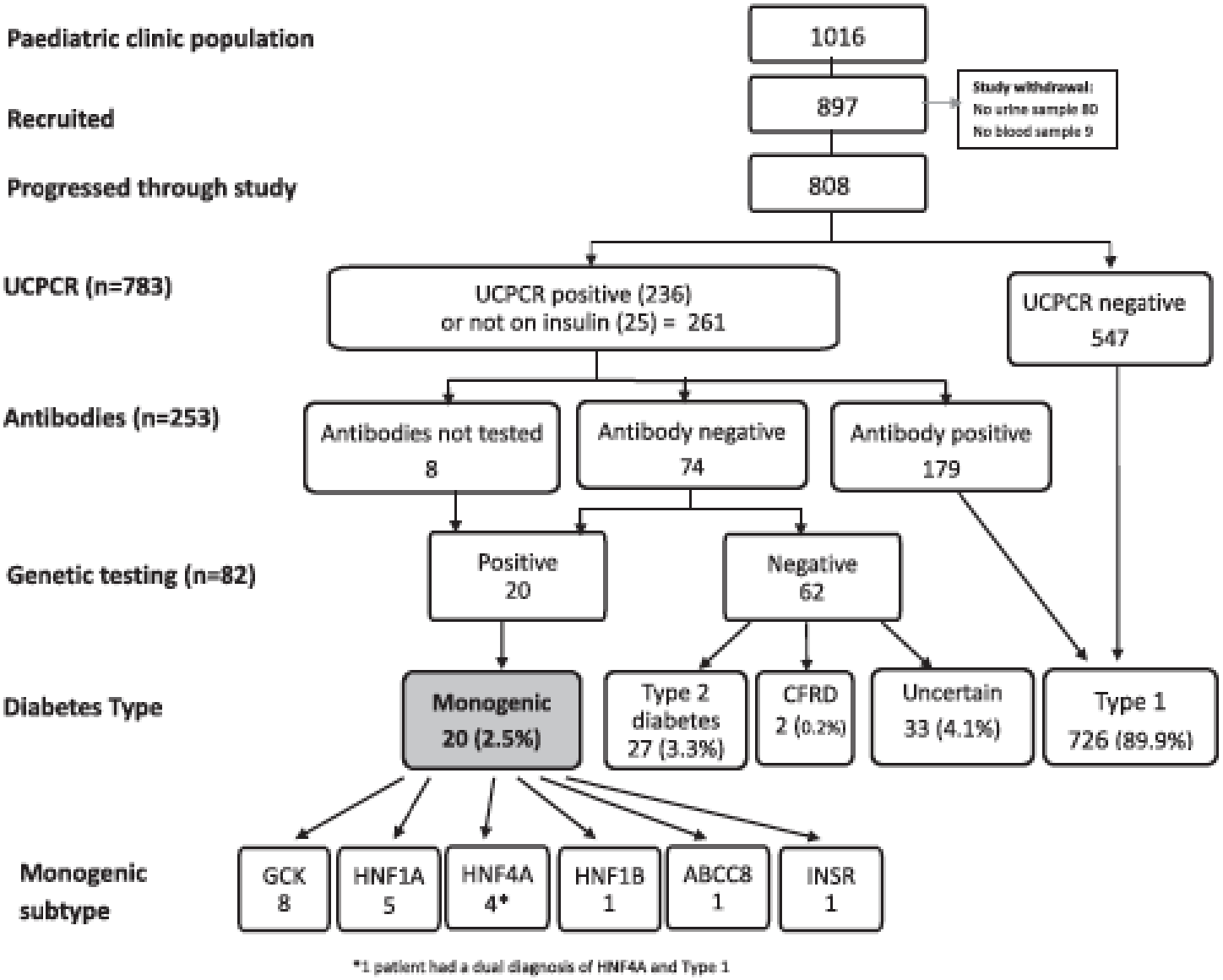
	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

Effects of age on progression to type 1 diabetes



Diabetes Care 2018;41:653–661 | https://doi.org/10.2337/dc17-0806

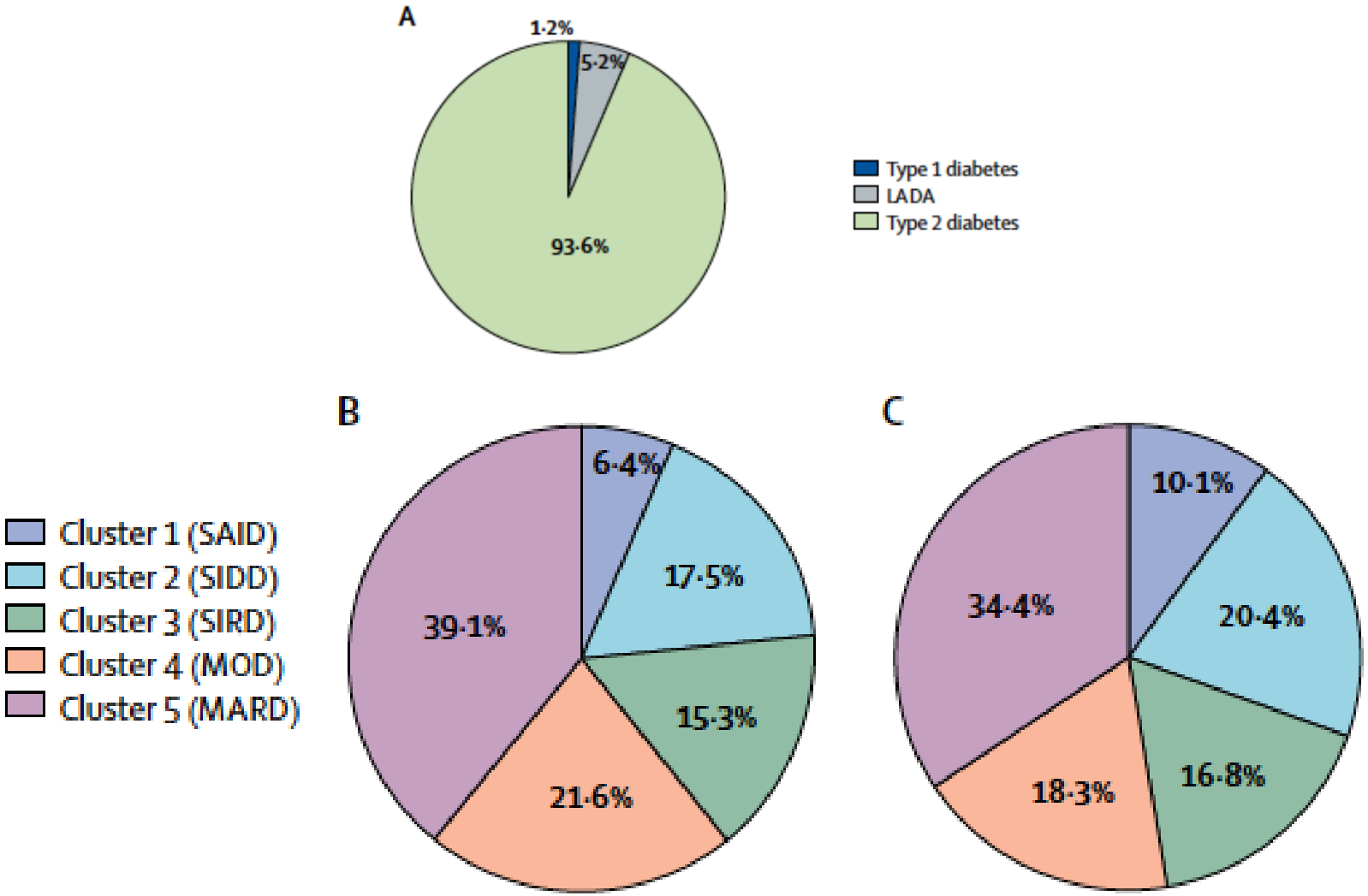
Screening for MODY in UK diabetic pediatric population



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

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*



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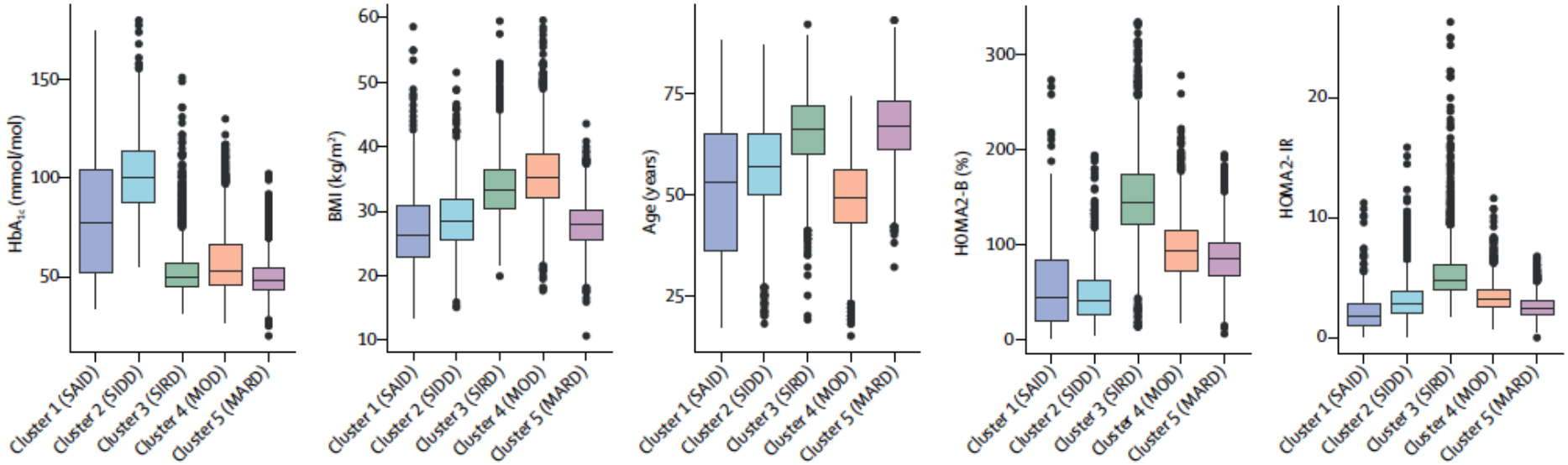

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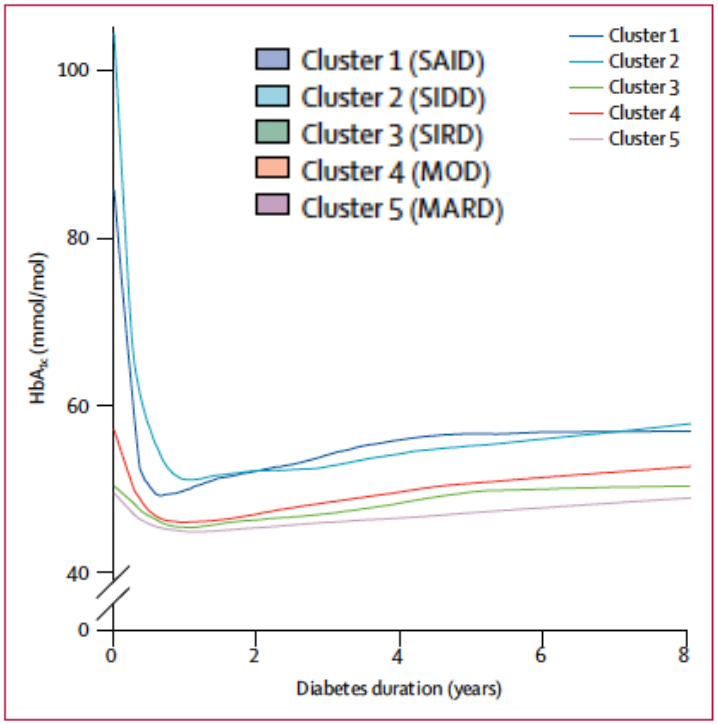

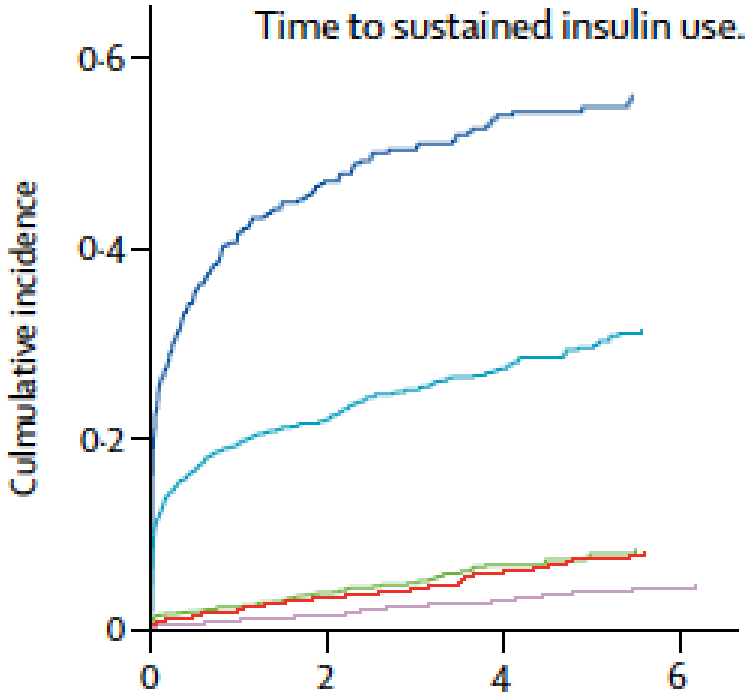

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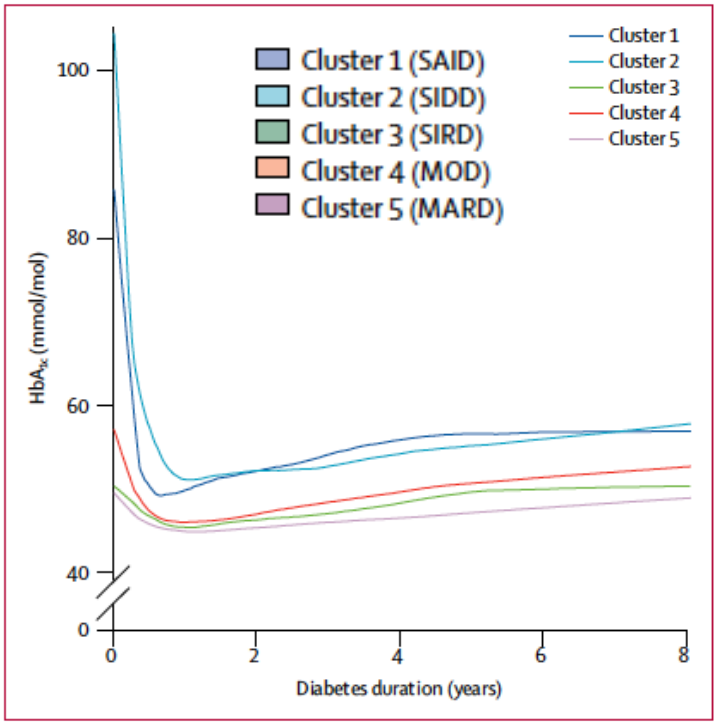

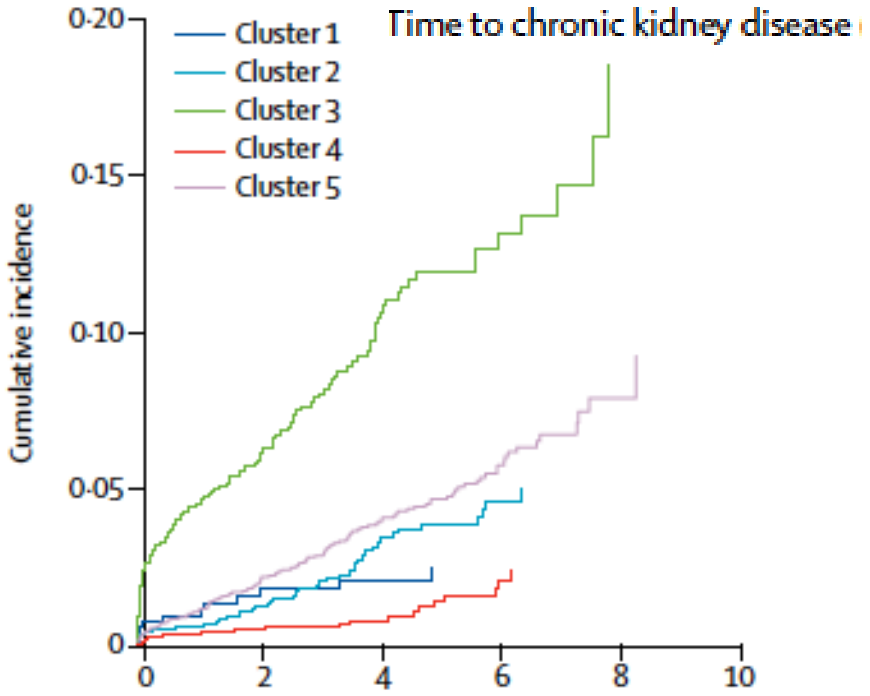

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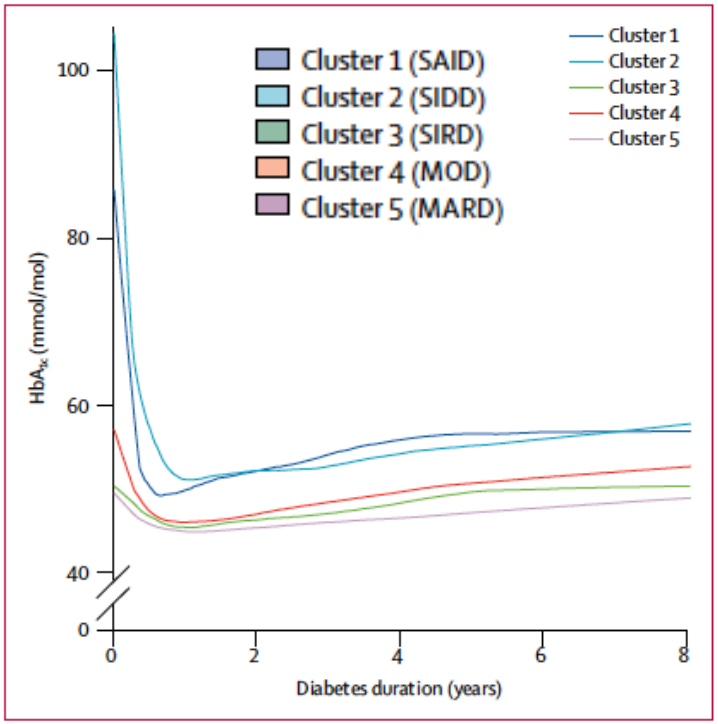

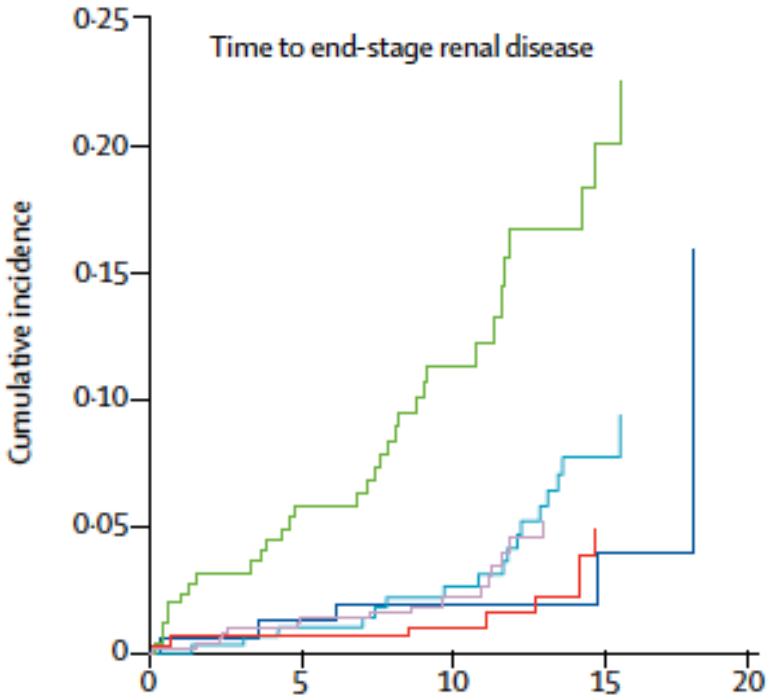

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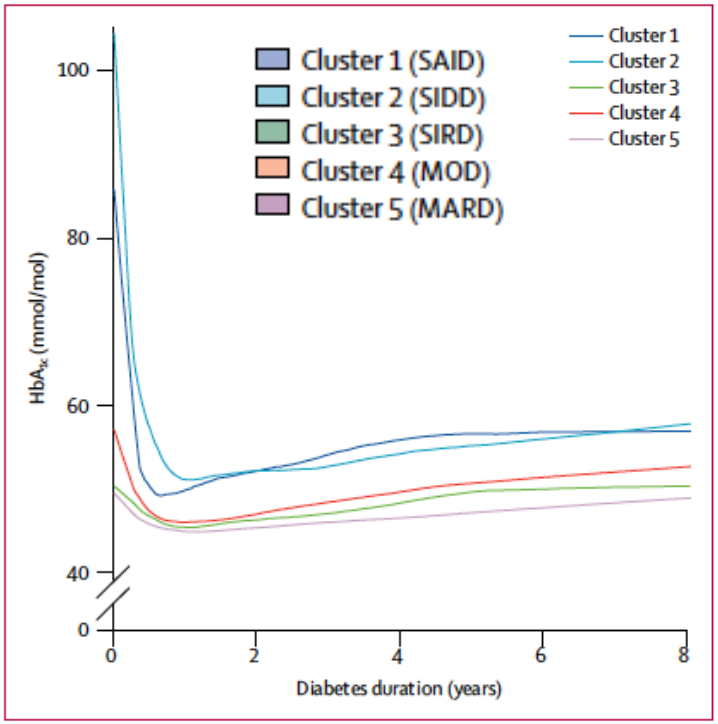

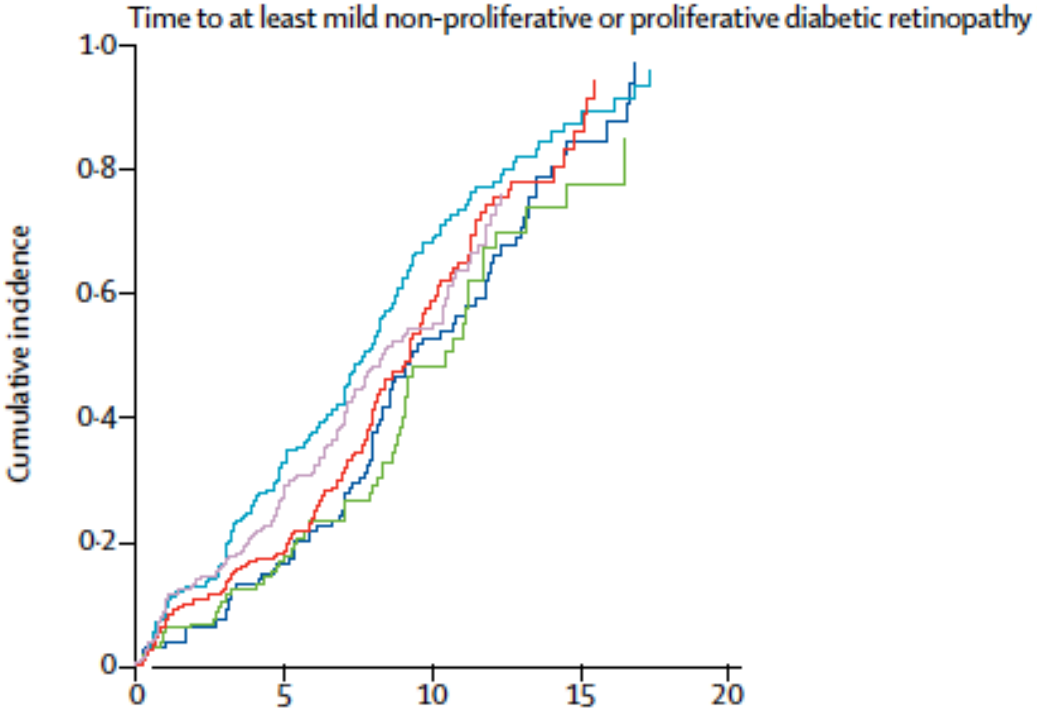

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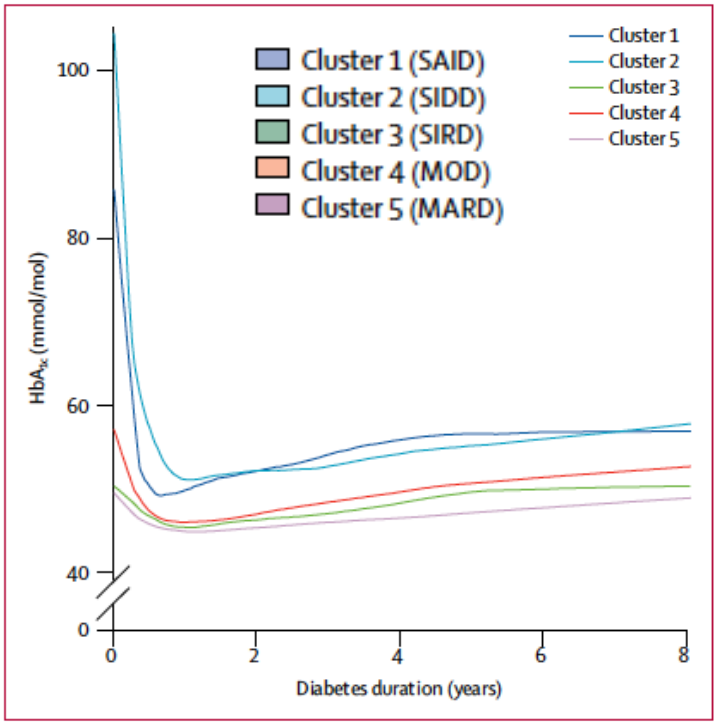
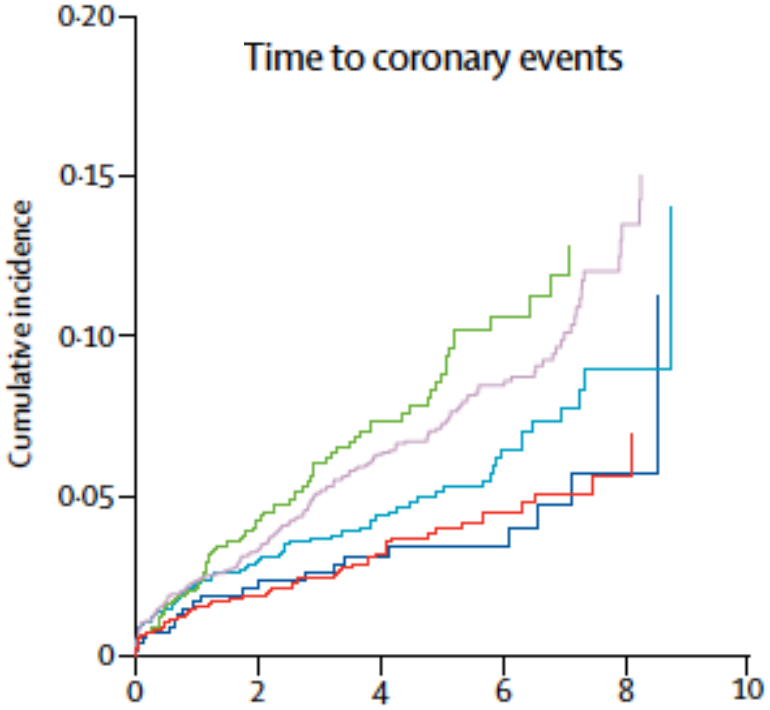




"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

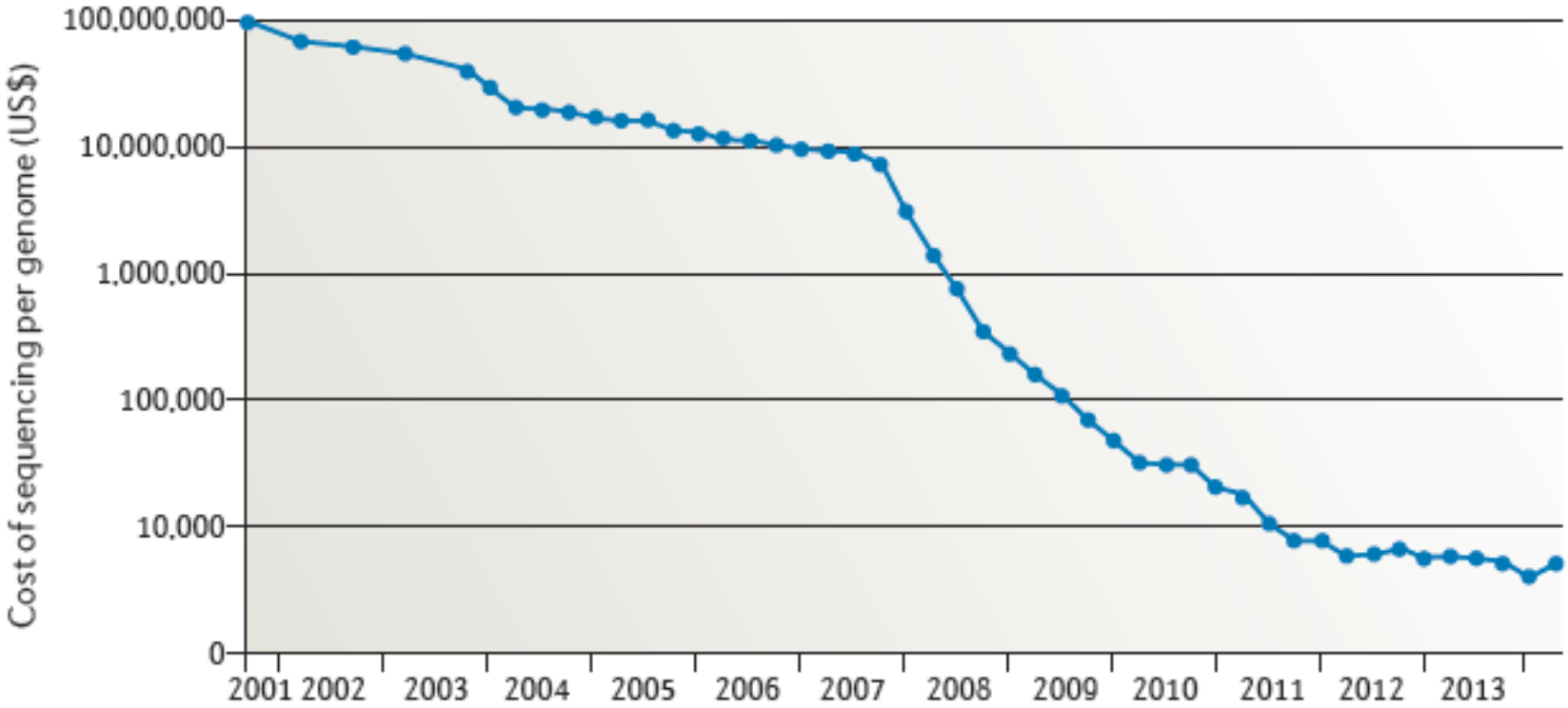
— President Barack Obama, State of the Union Address, January 20, 2015

Che cos'è la Precision Medicine

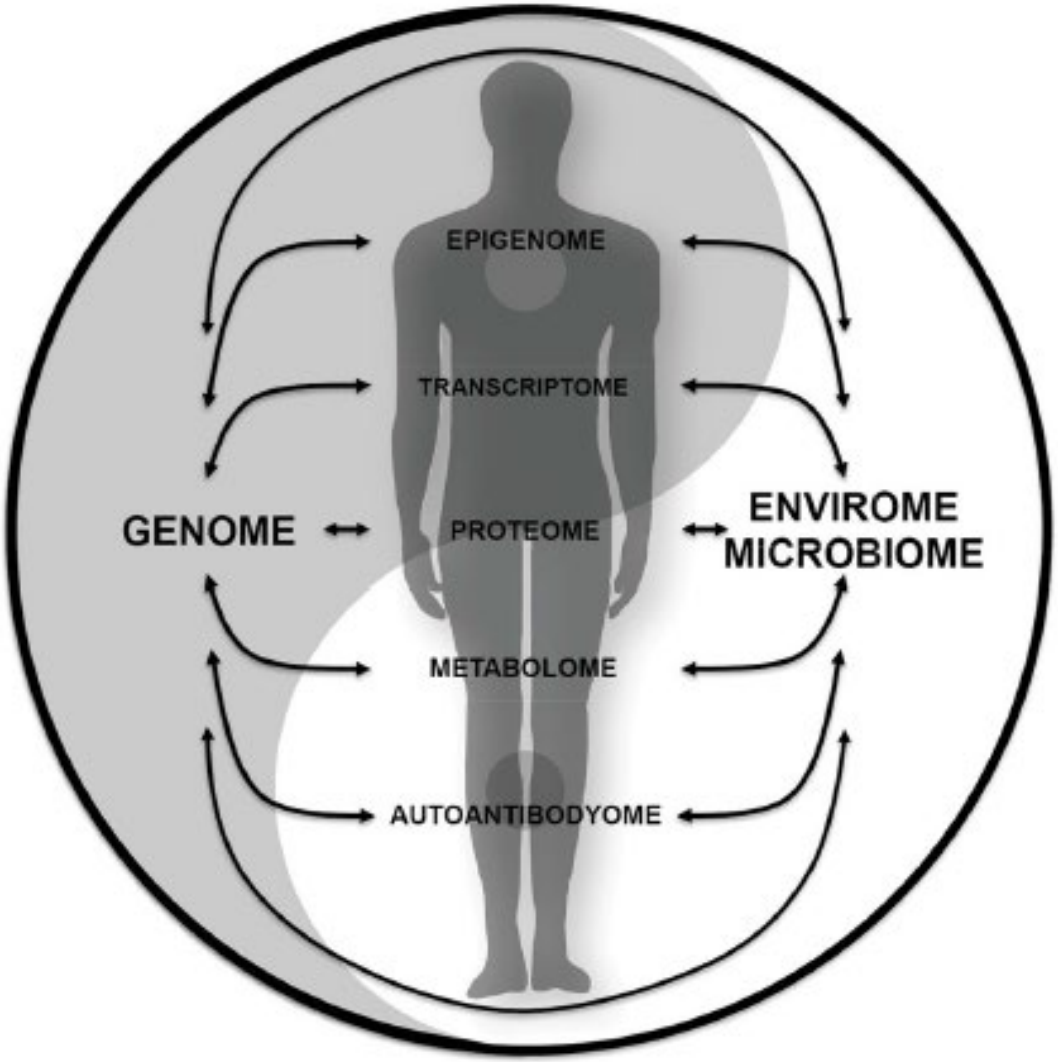
La **Precision Medicine** è un paradigma innovativo per la prevenzione, la diagnosi e la cura di patologie secondo un approccio personalizzato che tenga conto delle variazioni individuali del patrimonio genetico, dell'ambiente e dello stile di vita.

La Precision Medicine è oggi considerata la frontiera delle scienze mediche dove nei prossimi anni avverrà la sfida tecnologica e di conoscenze che trasformerà la terapia e i processi diagnostici, anche mediante l'identificazione di nuovi marcatori diagnostici e terapeutici per malattie neoplastiche, metaboliche, degenerative e genetiche

Il costo per sequenziare un genoma



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

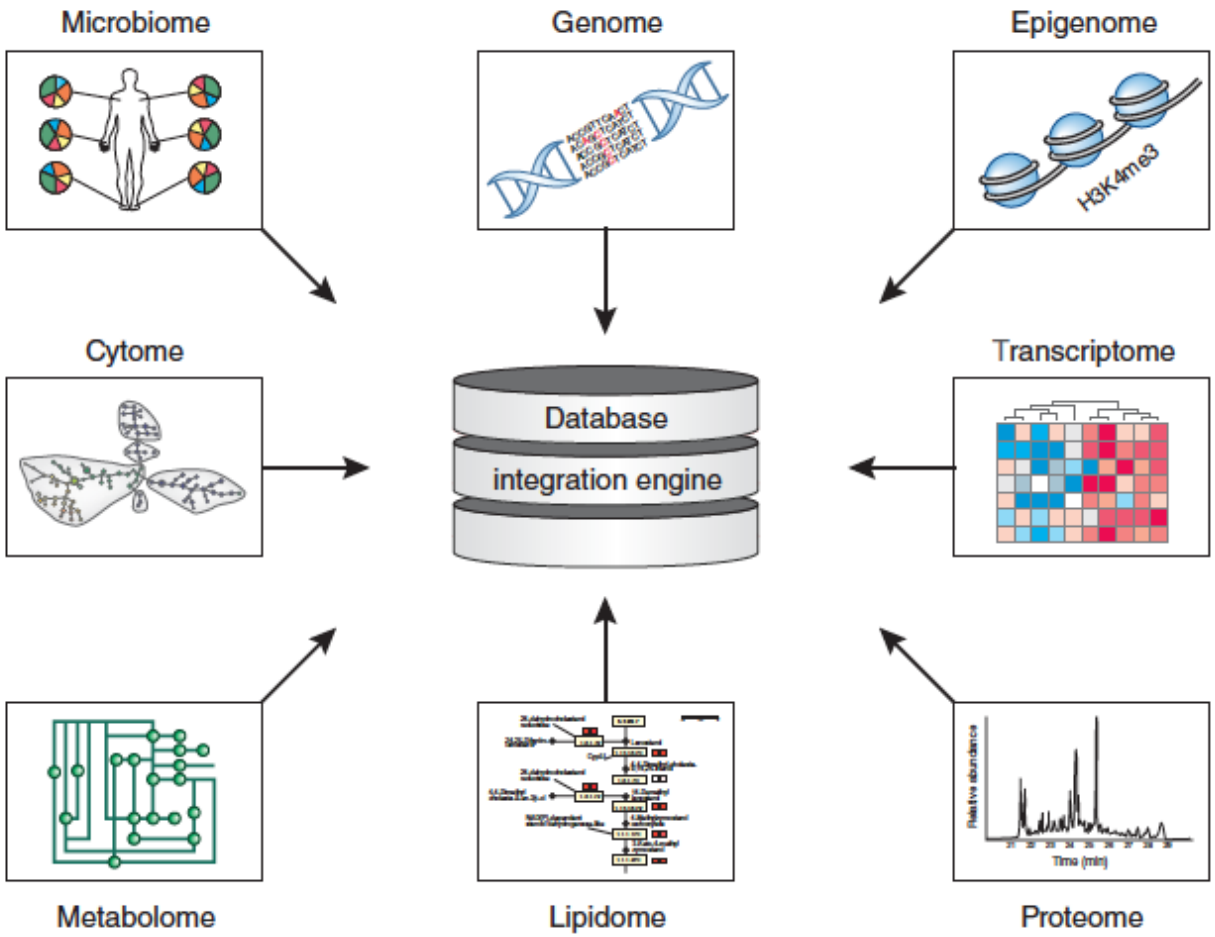


Si può parlare di nuova era della **Precision Medicine** perché oggi possiamo contare su:

✓Database biologici su larga scala;

✓Potenti strumenti di caratterizzazione "omica" del paziente;

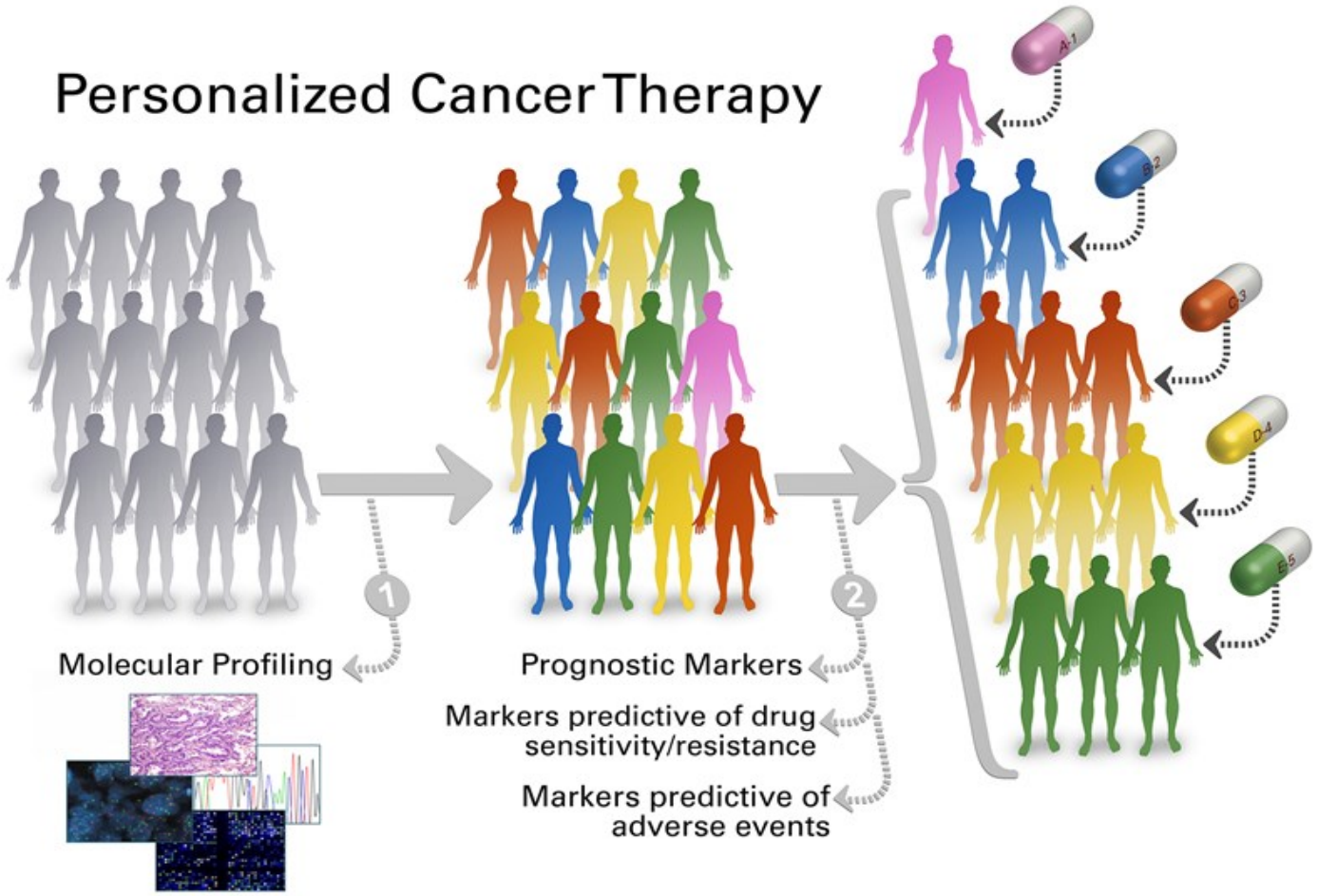
✓Strumenti informatici per la gestione di *Big Data*;

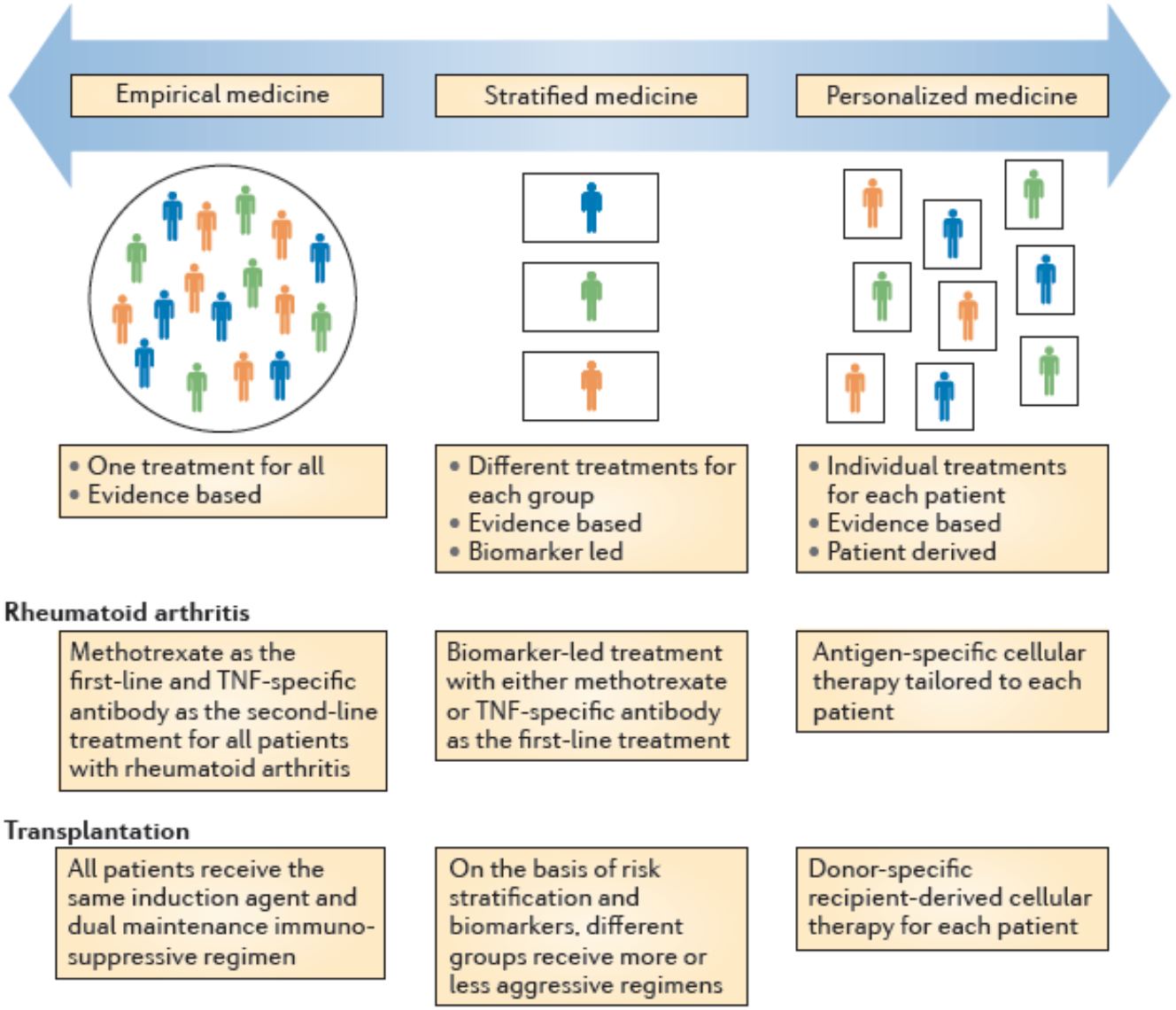


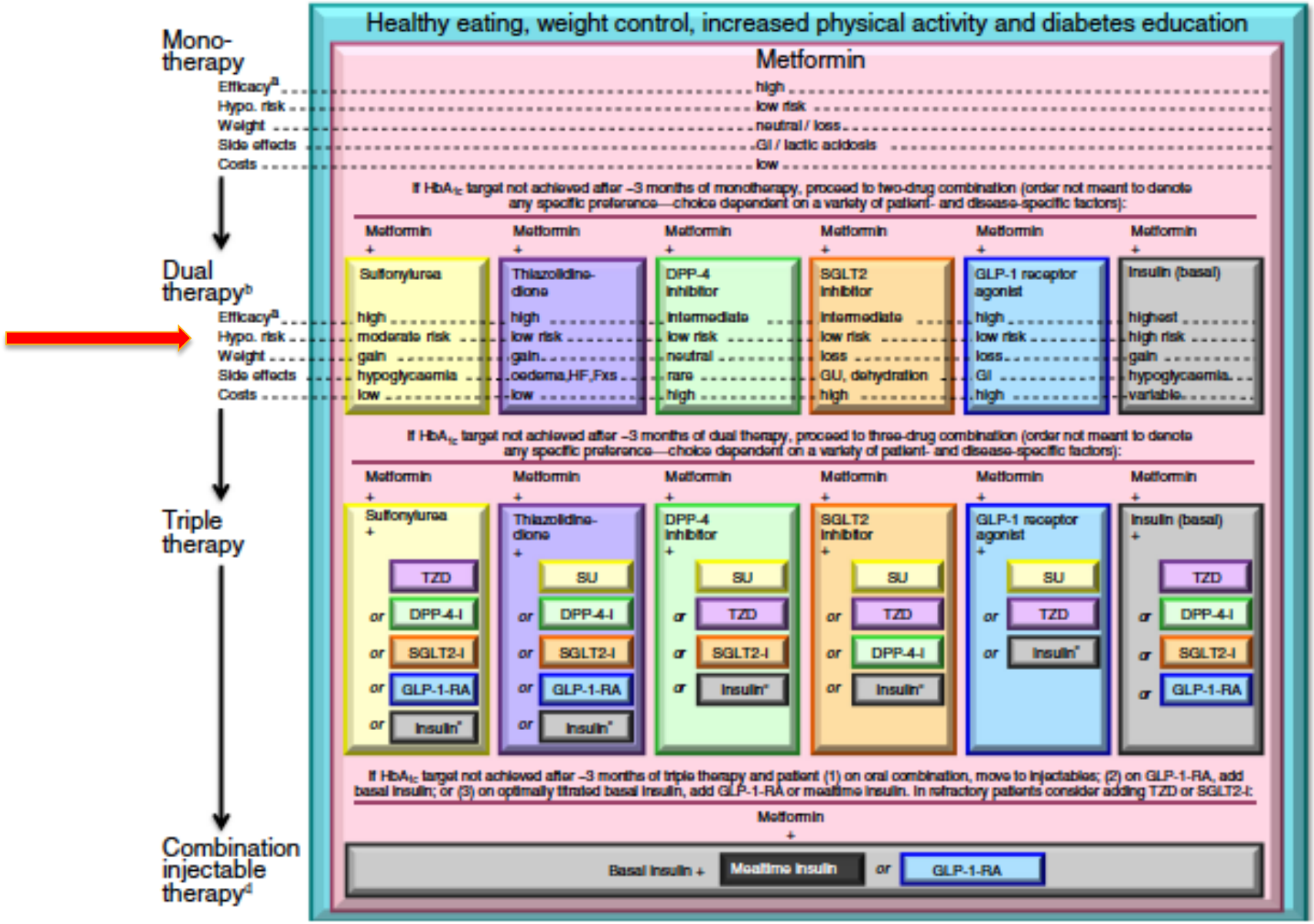
Nat.Rev.Immunol., doi:10.1038/nri3820 , March 2015

Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib[4]
	Lung cancer	EML4-ALK	Crizotinib[3]
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs[5]
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy[6]
Cardiovascular disease	Coronary artery disease	*CYP2C19*	Clopidogrel[7]
Pulmonary disease	Cystic fibrosis	*G551D*	Ivacaftor[8]
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs[9]
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents[10]
Endocrine disease	Multiple endocrine neoplasia type 2	*RET*	Prophylactic thyroidectomy[11]
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins[12]
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy[13]
Psychiatry	Alcohol-use disorder	*GRIK1*	Topiramate[14]
Pharmacogenomics	Smoking cessation	*CYP2A6*	Varenicline[15]
Ophthalmology	Leber's congenital amaurosis	*RPE65*	Gene therapy[16]


Personalized Cancer Therapy
A-1
B-2
C-3
D-4
E-5
1
2
Molecular Profiling
Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events


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

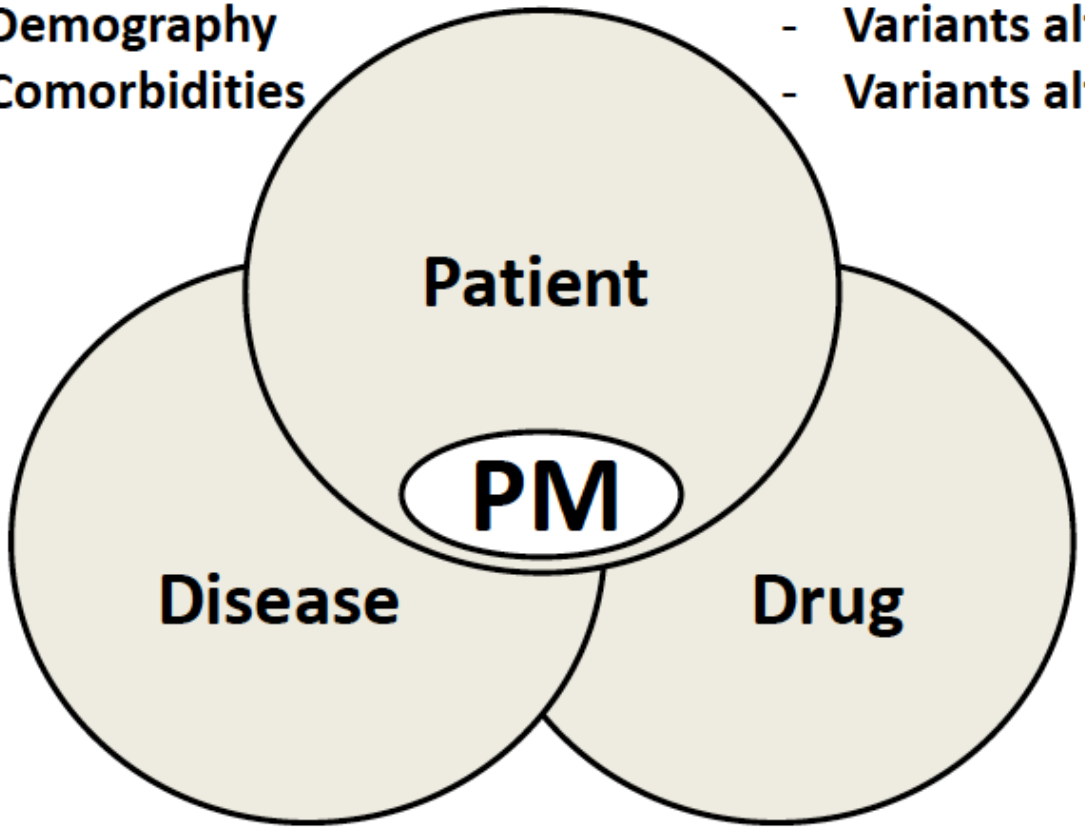


Diabetes Care, Diabetologia. 2015

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

The Impact of Precision Medicine in Diabetes: A Multidimensional Perspective

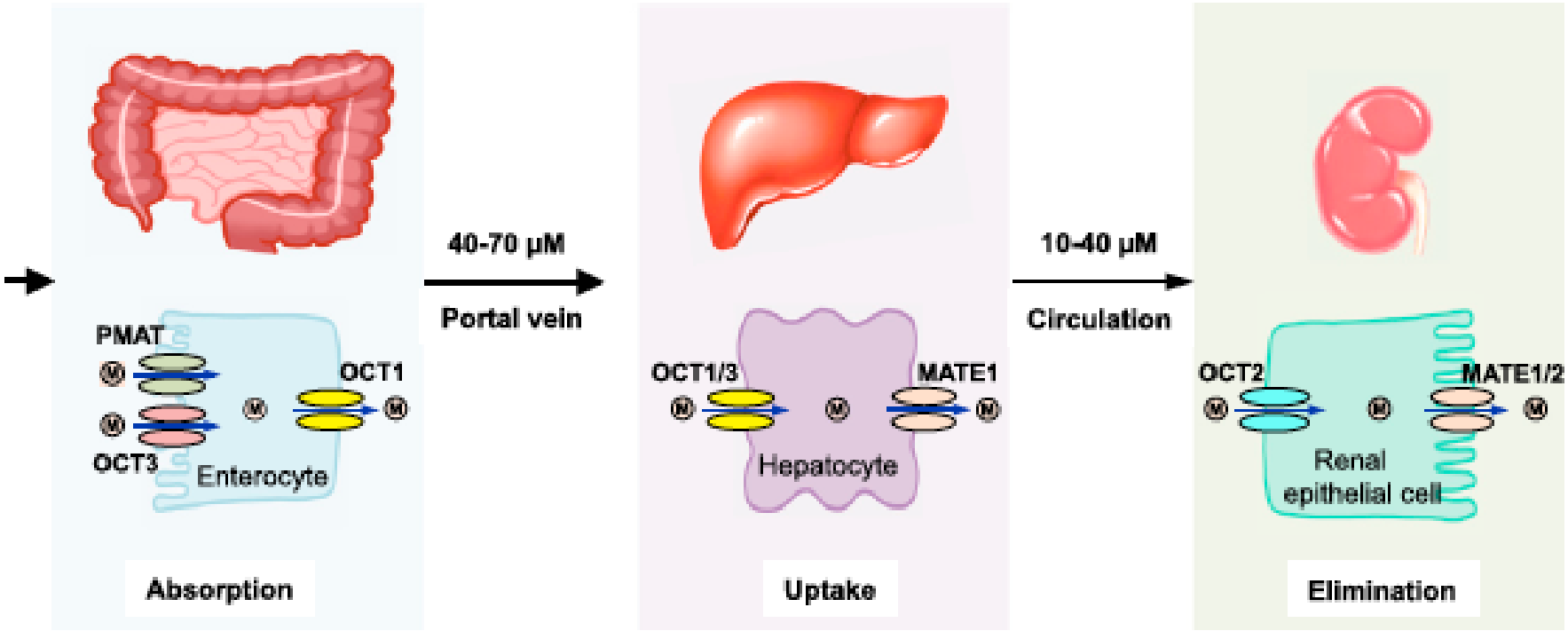
Stephen S. Rich[1] and William T. Cefalu[2]

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

Farmacogenomica e risposta 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

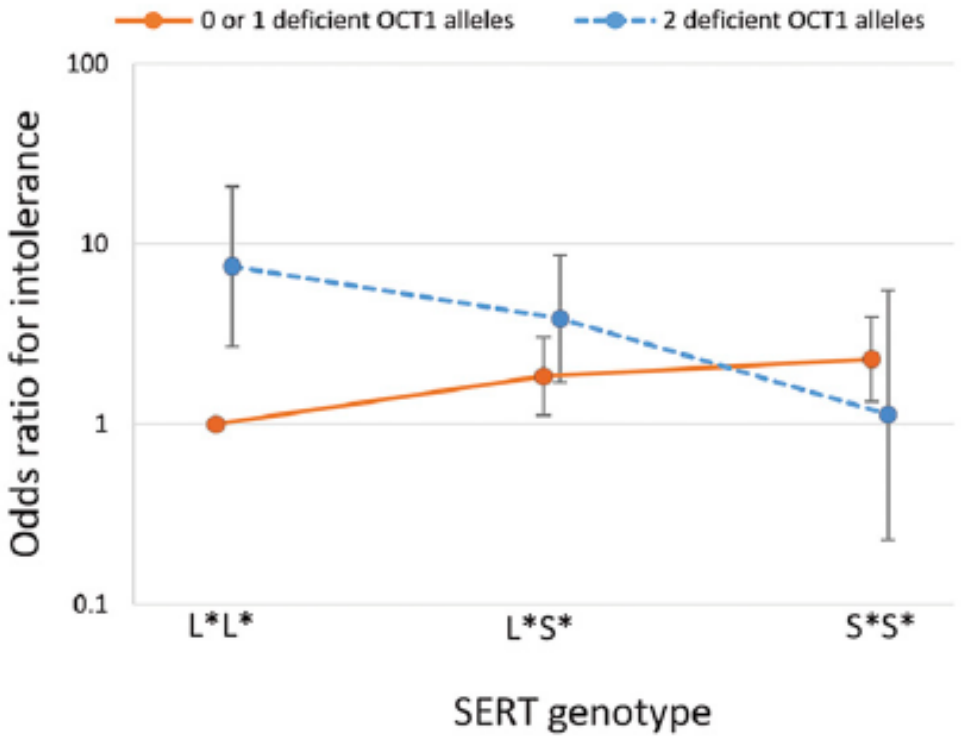


Cell Metabolism 21, February 3, 2015

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

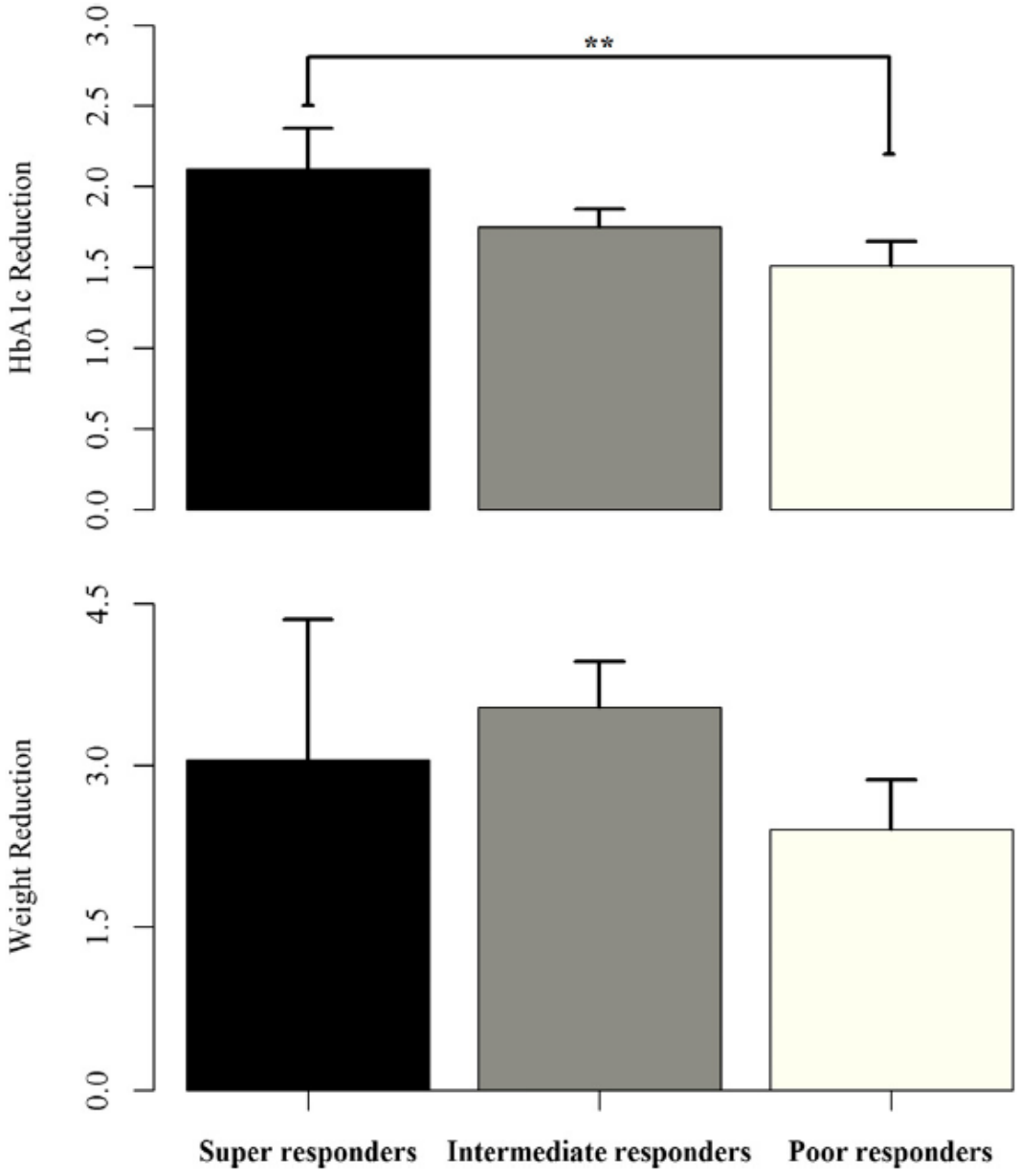


Numbers of intolerant/tolerant individuals

	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

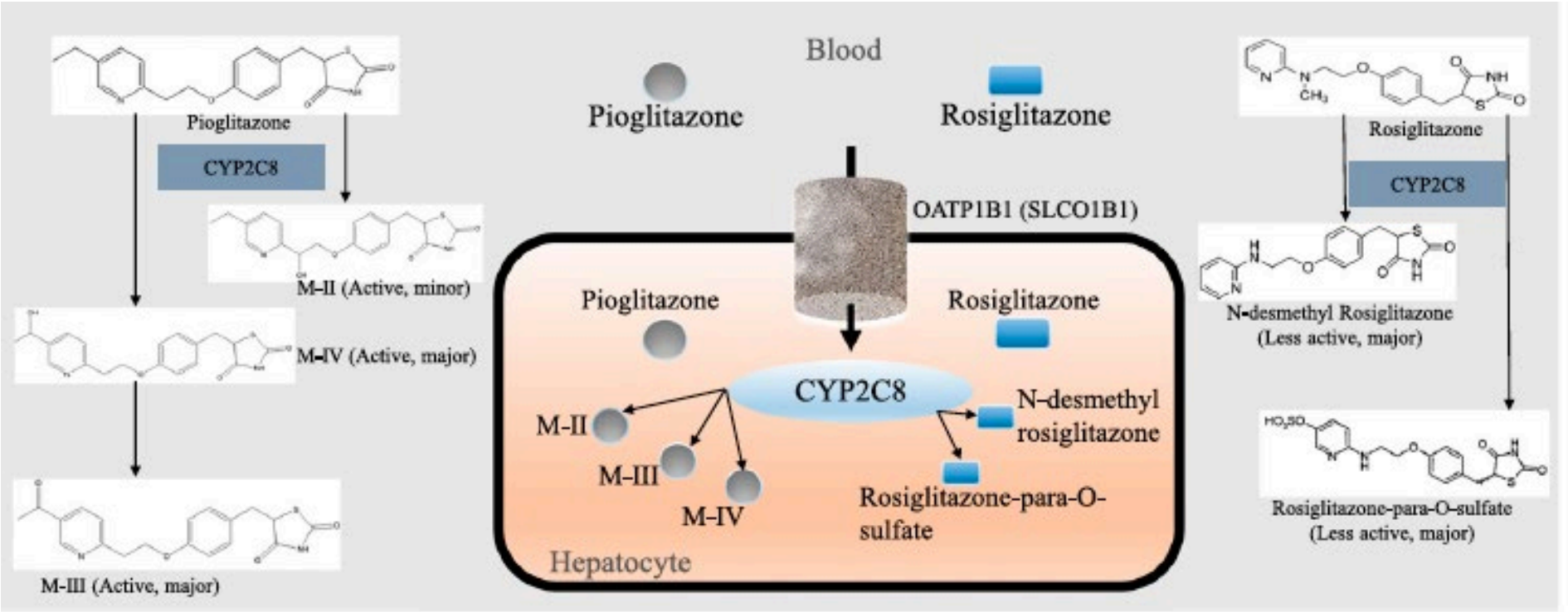
Diabetes Care



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



Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-Term Glycemic Response to DPP-4 Inhibitor Therapy

John M. Dennis,[1] Beverley M. Shields,[2] Anita V. Hill,[2] Bridget A. Knight,[2] Timothy J. McDonald,[2,3] Lauren R. Rodgers,[1] Michael N. Weedon,[4] William E. Henley,[1] Naveed Sattar,[5] Rury R. Holman,[6] Ewan R. Pearson,[7] Andrew T. Hattersley,[2] and Angus G. Jones,[2] on behalf of the MASTERMIND consortium

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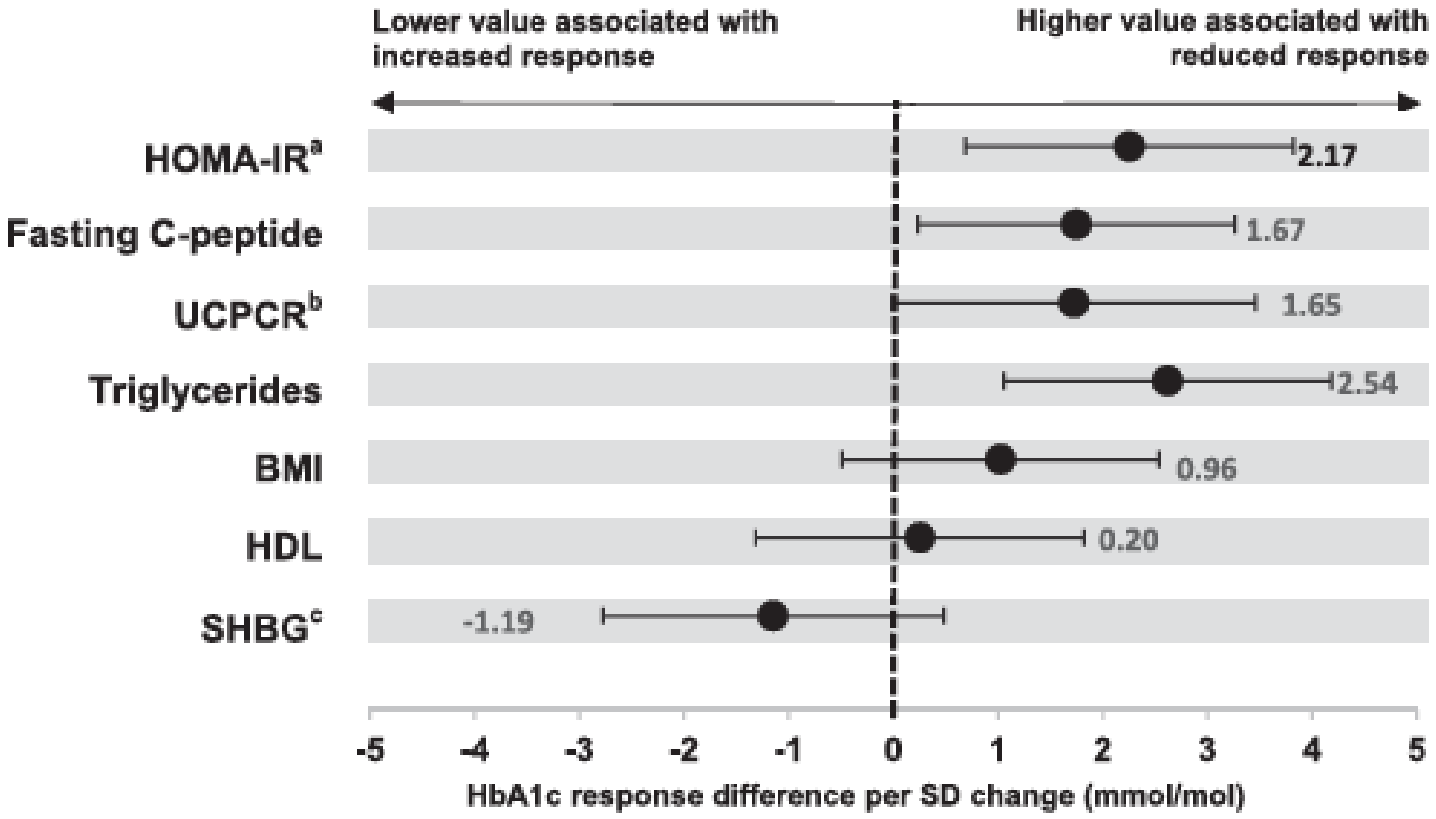

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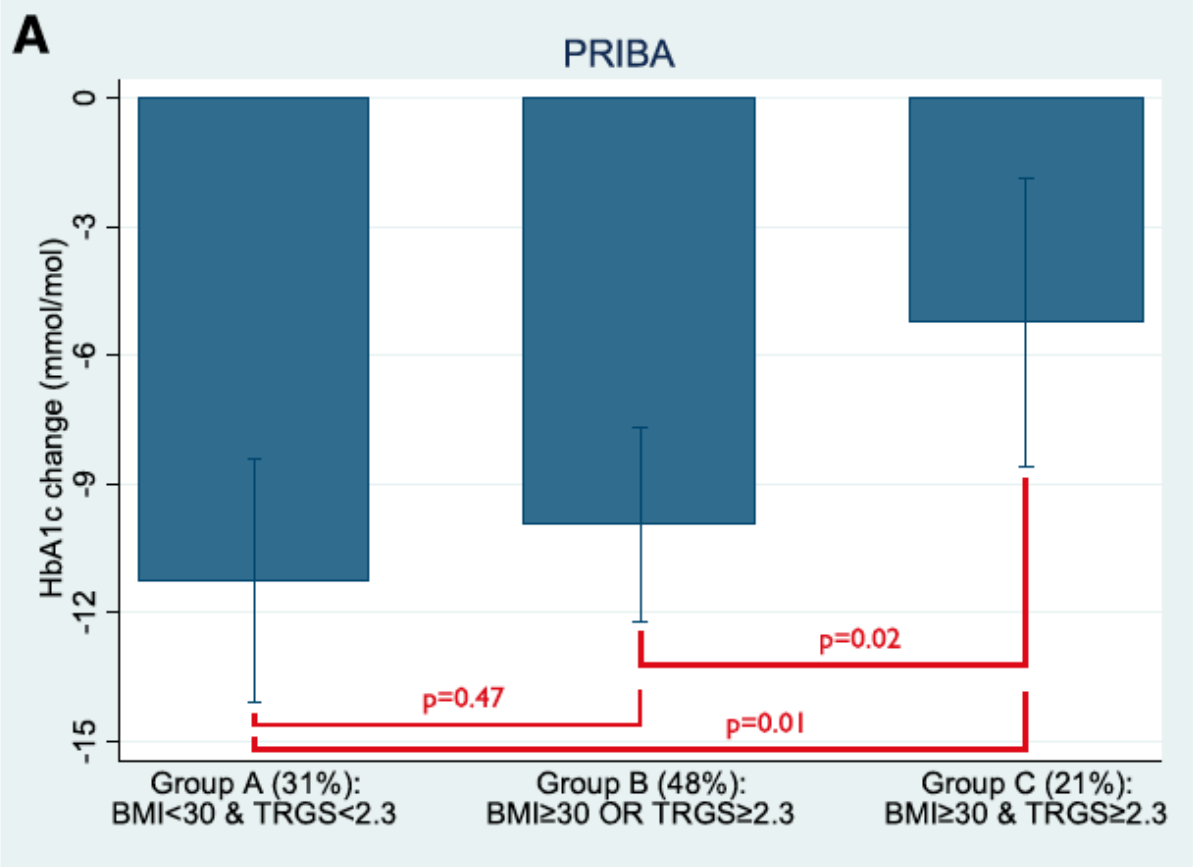
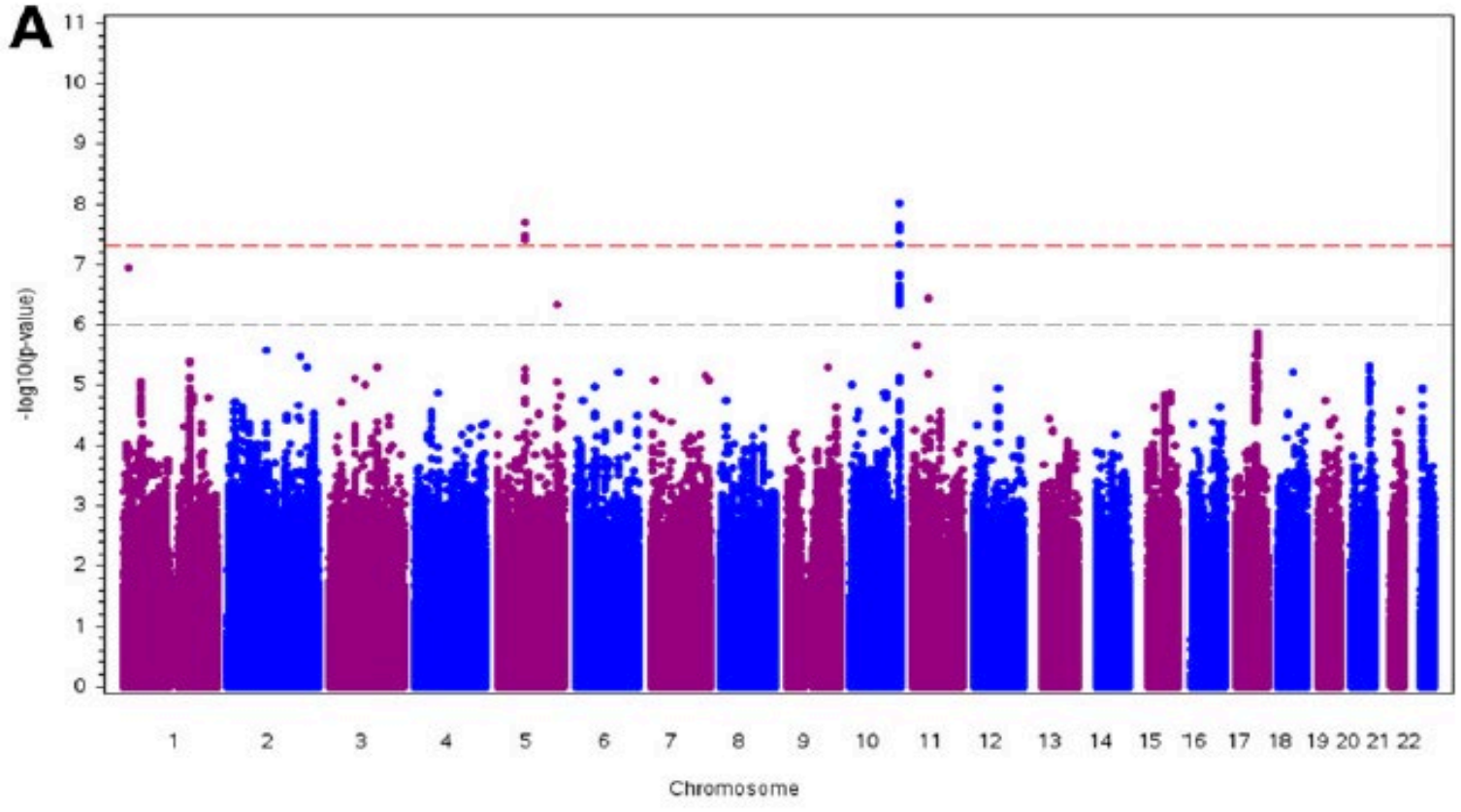


Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Control in Type 2 Diabetes: Findings From the ACCORD Clinical Trial

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.



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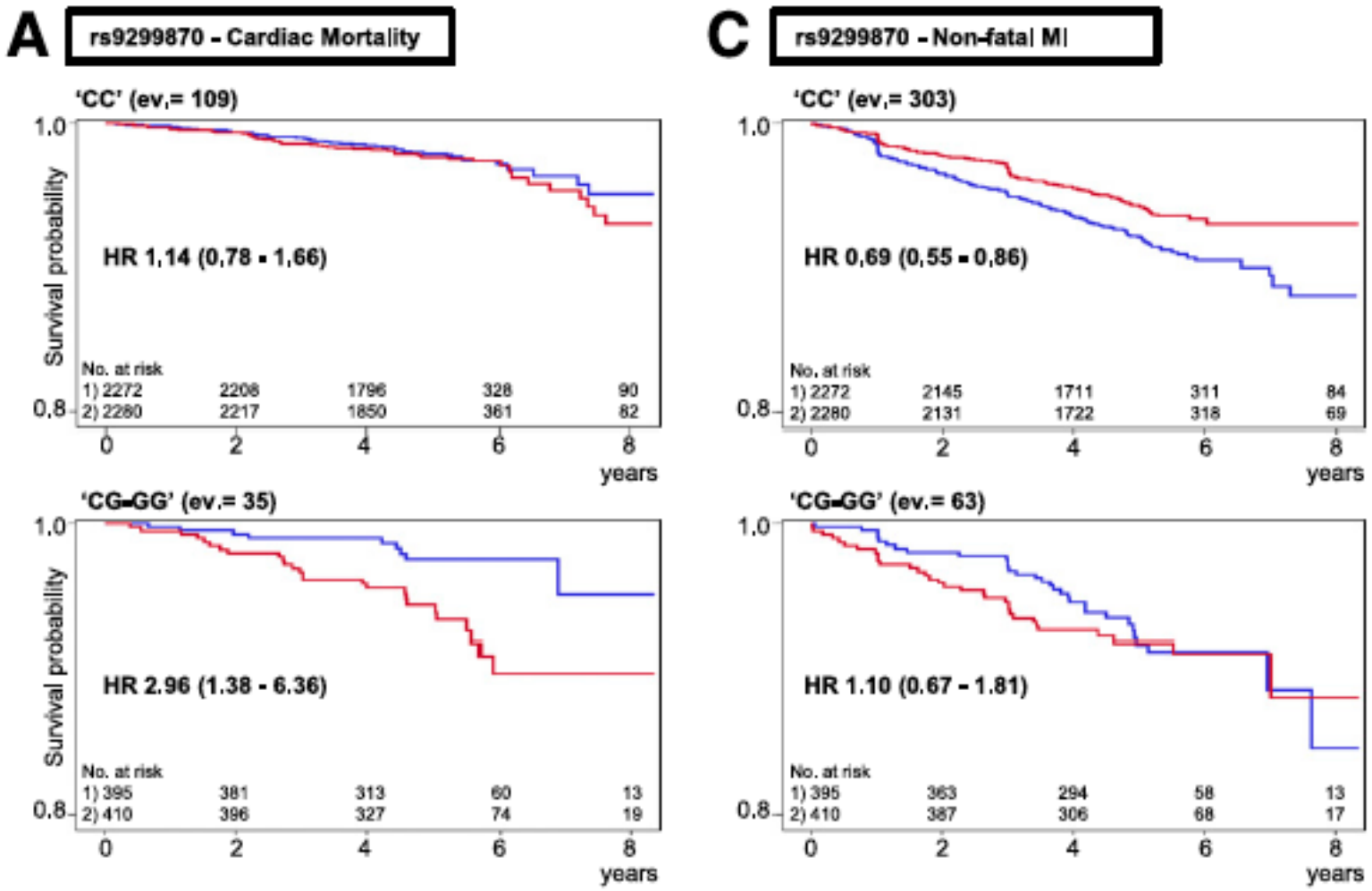
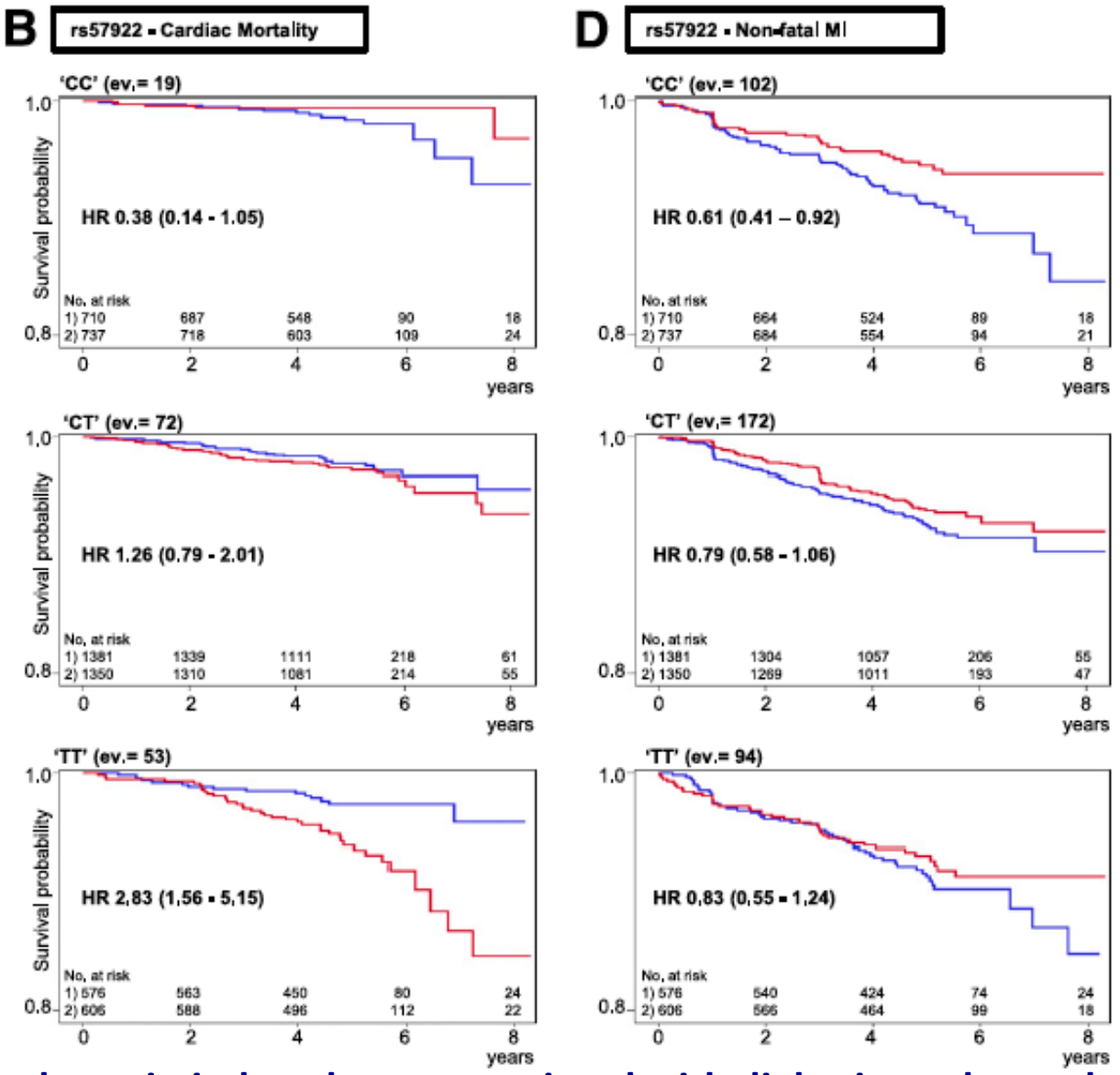


MGMT functions as a negative regulator of ESR1 (estrogen receptor 1)

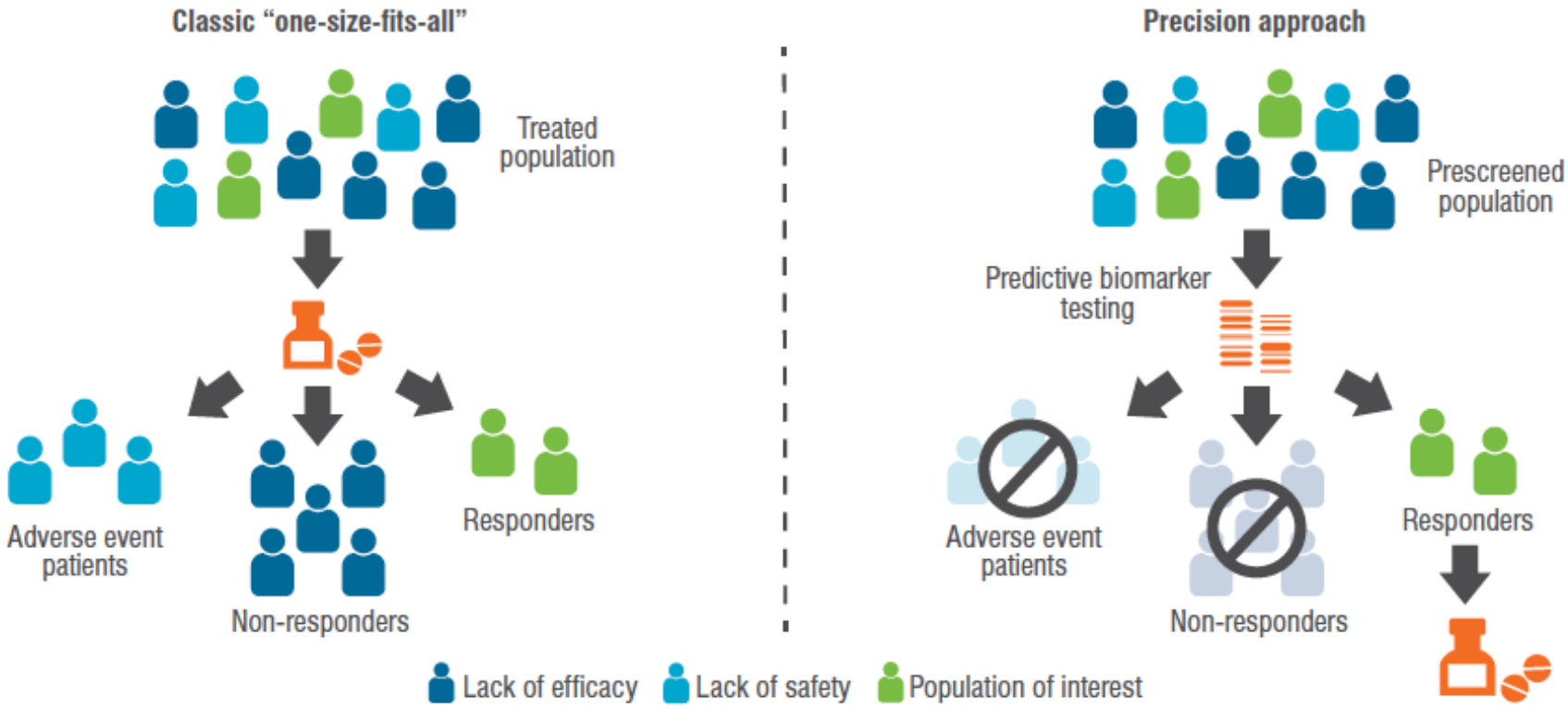
Two genetic loci, at 10q26 and 5q13, predict the cardiovascular effects of intensive glycemic control in ACCORD



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

Changing how drugs are delivered

Identify non-responders and safety issues before prescribing or treating



Precision Medicine: Azioni da intraprendere

L'obiettivo generale, pertanto, è quello di creare un ecosistema di **Precision Medicine** che metta in relazione i soggetti (pazienti, clinici, ricercatori) e le piattaforme di riferimento (laboratori clinici e di ricerca, biobanche, database, le infrastrutture informatiche di gestione e analisi dei dati) e che miri alla condivisione delle conoscenze e a fornire, attraverso il Sistema Sanitario, strumenti efficienti ed efficaci di screening diagnosi e cura a servizio del cittadino.

La ricerca clinica e sperimentale che si svolge presso l'Università di Siena in collaborazione con l'Azienda Ospedaliera Universitaria Senese (AOUS) e con la Fondazione Toscana Life Sciences (TLS) costituisce una delle attività di punta del nostro Policlinico e dell'area biomedica dell'Ateneo di Siena, riconosciuta a livello regionale, nazionale ed internazionale, come dimostrato dal notevolissimo numero di progetti di ricerca finanziati da numerosi enti pubblici e privati e di trials clinici condotti e coordinati negli ultimi anni.

Aree di eccellenza comprendono, tra le altre, le ricerche nel campo:

- **Vaccini, malattie infettive, infiammatorie ed immuno-mediate**
- **Oncologia (diagnosi, terapia), ematologia, trapianti**
- **Neuroscienze, invecchiamento e patologie neurodegenerative**
- **Malattie endocrine, metaboliche, cardiovascolari**
- **Malattie rare**
- **Farmacologia**

Centro di Medicina di Precisione a Siena

- **L'obiettivo: creare a Siena, un polo scientifico e tecnologico che, basandosi sulla Precision Medicine e attraverso la condivisione di competenze, laboratori e piattaforme tecnologiche, promuova gli investimenti con immediate ricadute positive sul servizio sanitario regionale in termini di accesso a prodotti e servizi innovativi e di abbattimento dei costi per la diagnosi e la cura.**
- **La creazione di una piattaforma integrata ad accesso aperto che consenta a organismi di ricerca e alle imprese di sviluppare le proprie progettualità condividendo competenze, strutture e risorse e mettendole al servizio del sistema sanitario regionale.**

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TOSCANA LIFE SCIENCES

Centro di Medicina di Precisione a Siena

Obiettivi specifici

- **Realizzare piattaforme tecnologiche integrate e potenziare quelle già esistenti**
- **Bio-Banca**
- **Istituire e standardizzare un sistema integrato di Bioinformatica e Big data management per la raccolta e la strutturazione dei dati;**
- **Supportare progetti innovativi di ricerca e sviluppo che possano realizzarsi utilizzando le suddette piattaforme.**
- **Favorire la ricerca traslazionale e la qualificazione delle attività di sperimentazione clinica attraverso:**

1) La standardizzazione delle pratiche dei ricercatori coinvolti in sperimentazione cliniche nazionali/internazionali;

2) l'innovazione delle procedure;

3) l'integrazione interdipartimentale di gruppi di ricerca

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.