

# **LABORATORIO, ...TRIAL CLINICI .....REAL LIFE**

*Congresso Congiunto AMD-SID Piemonte e Valle d'Aosta  
Sinergie per l'Innovazione  
Torino 3 dicembre 2016*



**Gabriella Gruden**

*Dipartimento di Scienze Mediche  
Università di Torino*



# IL LUNGO VIAGGIO ...



**RICERCA DI BASE**

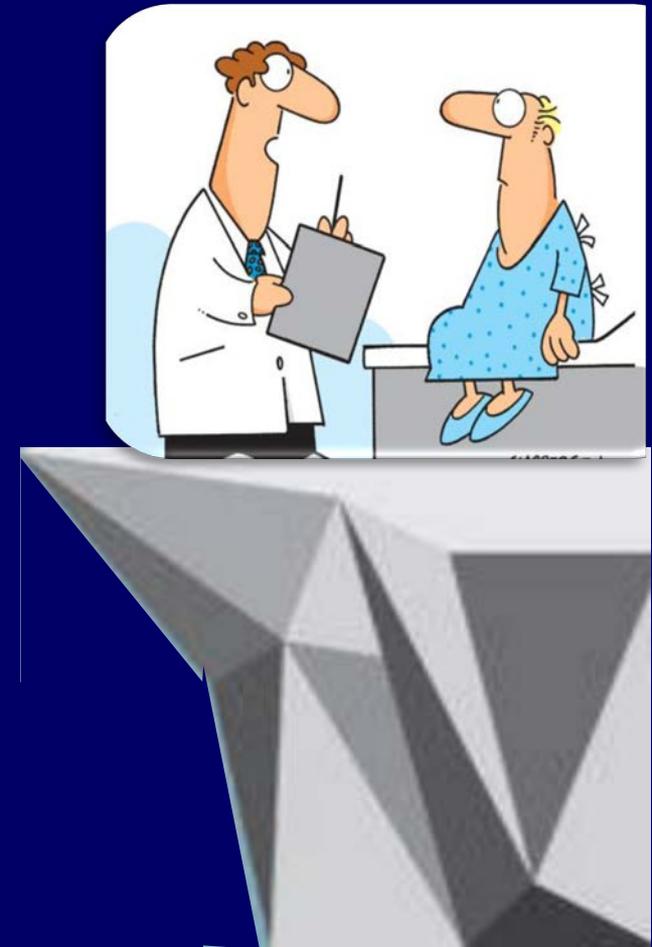


**TRIALS  
CLINICI**

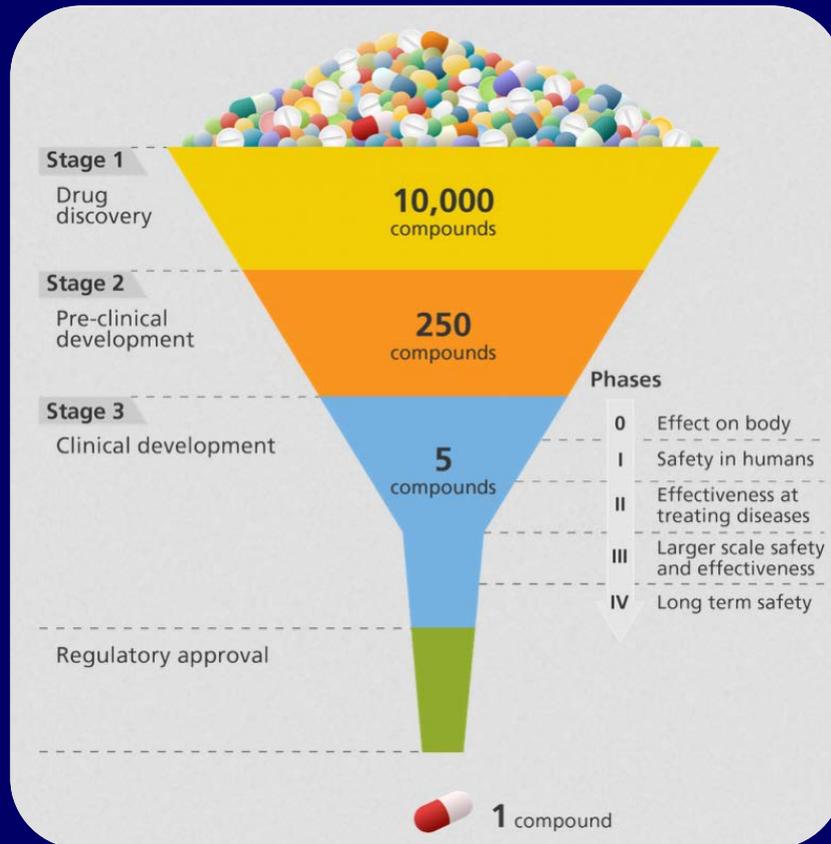


**PRATICA  
CLINICA**

# ***“GAP” TRA RICERCA E ....PRATICA CLINICA***



# SVILUPPO DI UN FARMACO

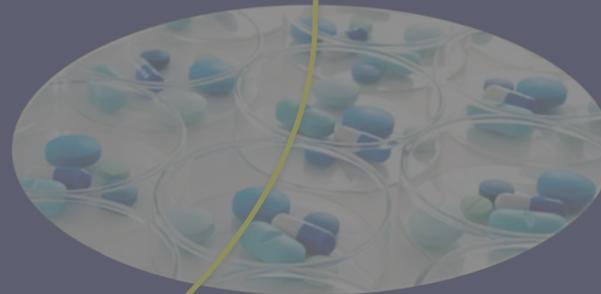


- Tempi: 10-20 anni
- Costi: \$\$\$\$
- Successo: < 4 su 1000

# IL LUNGO VIAGGIO ...



**RICERCA DI BASE**



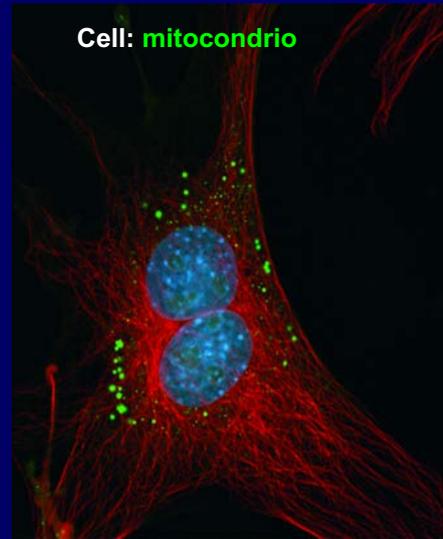
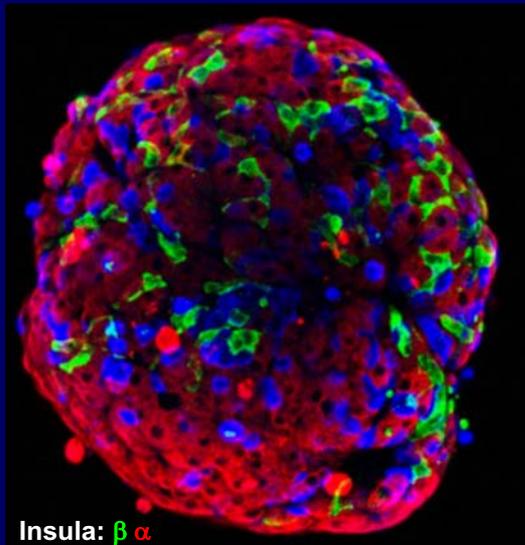
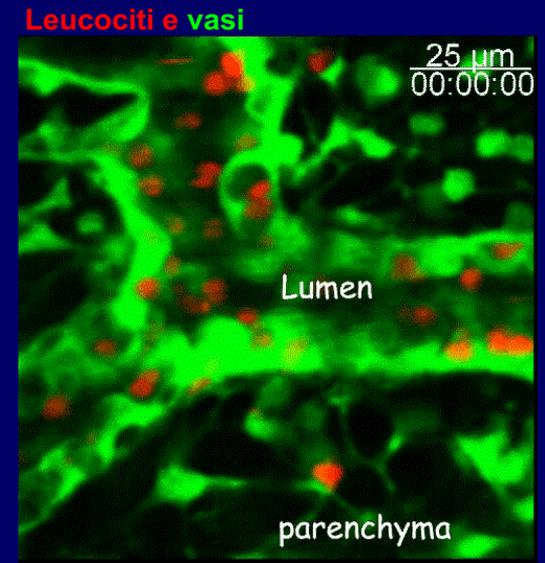
**RICERCA  
CLINICA**



**APPLICAZIONE  
nella PRATICA  
CLINICA**

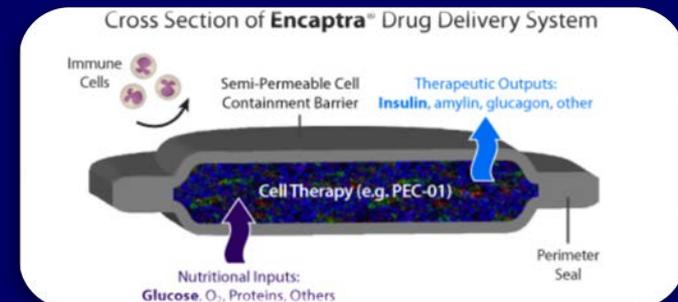
# RICERCA DI BASE

- Time lapse
- Nano-microscopia



## Stem Cells Rigenerativa

- DM
- compicanze



# EDITING GENETICO ED OMICHE

## CRISPR CAS9

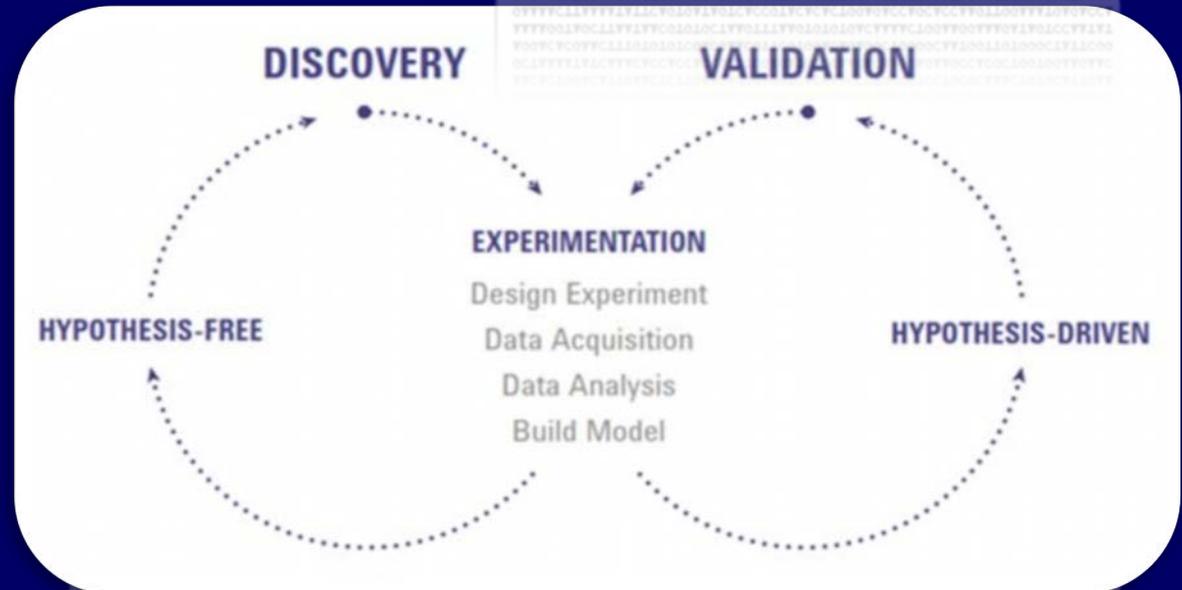
- Editing genetico



```
den1.fasta - WordPad
File Edit View Insert Format Help
>gi|9626685|ref|NC_001477.1| Dengue virus type 1, complete genome
AGTTGTTAGTCTACGTGGACCGACAAGAACGTTTCGAATCGGAAGCTTGCTTAAAGTGTCTAACAGT
TTTTTATTAGAGAGCAGATCTCTGATGAACAACCAACGGAAAAAGCGGGTCGACCGCTTTTCAATATGC
TGAAACGGCGGAGAAACCGCGTGTCAACTGTTTACAGTGGGGAAGAGATTCTCAAAAAGGATTCCTTC
AGGCCAAGGCCCATGAAATGGGTGATGGCTTTTATAGCATTTCCTAAGATTCTTAGCCATACCTCCAACA
GCAGGAATTTGGCTAGATGGGGCTCATTCAAGAAATGAGGCGATCAAGATGTTACGGGGTTTCAAGA
AAGAAATCTCAAAACATGTTGAACATAATGAACAGGAGGAAAAAGATCTGTGACCATGCTCCTCATGTGCT
GCCACAGCCCTGGCGTTCCATCTGACCACCCGGAGGGGGAACCGCGCATGATAGATTAGCAAGCAGGAA
AGAGGAAAATCACTTTTGTTTAAGACCTTGCAGTGTCAACATGTGCACCCTTATTGCAATGGATTGG
GAGAGTTATGTGAGGACACAATGACCTACAAATGCCCCCGGATCACTGAGACGGAAACCGAGATGACGTTGA
CTGTTGGTGCAATGCCACGGAGACATGGGTGACCTATGGAACATGTTCTCAAACTGGTGAACACCGGACGA
GACAAACGTTCCGTCGCACTGGCACCAACACAGTAGGGCTTGGTCTAGAACAAGAAACCGGAAACGGGATGT
CCTCTGAAGGGCGTTGGAAACAATAACAAAAGTGGAGACCTGGGCTCTGAGACACCCAGGATTCACGGT
GATAGCCCTTTTTCTAGCACATGCCATAGGAACATCCATCACCCAGAAAAGGATCATTTTTTTTGCTG
ATGCTGGTAACTCCATCCATGGCCATGCGGTGGGAAATAGGCAACAGAGACTTCGTGGAAAGGACTGT
CAGGAGCTACGTGGGTGGATGTGGTACTGGAGCATGGAAGTGGGCTACTACCATGGCAAAAAGACAAACC
AACTGGACATTTAACTCTTGAAGACGGAGGTCAAAACCCTGGCGTCTGGCGCAAACTGTGCATTGAA
GCTAAATAATCAAAACCCACACCGATTTCGAGTGTGCCAACAAAGGAGAGCCAGCGTGGTGGAAAGAC
AGGACAGAACTTTGTGTGACGACAACTTCGTGGACAGAGGGTGGGCAATGGTGTGGGCTATTCCGG
AAAAAGTACGTTAATACCTGTGCTAAGTTTAACTGTGTGACAAAACCTGGAAGGAAAGATAGTCCAATAT
GAAAACCTAAAATATTTCAGTATAGTACCGGTACACACTGGAGACCAAGCACCAGTGGAAATGAGACCA
CAGAACATGGAAACAACTGCAACCAATAACACCTCAAGCTCCACGCTCGGAAATACAGCTGACAGACTACGG
AGCTCTAACATTGGATTGTTACCTAGAACAGGGCTAGACTTTAATGAGATGGTGTGTTGCAATGAA
```

## OMICHE

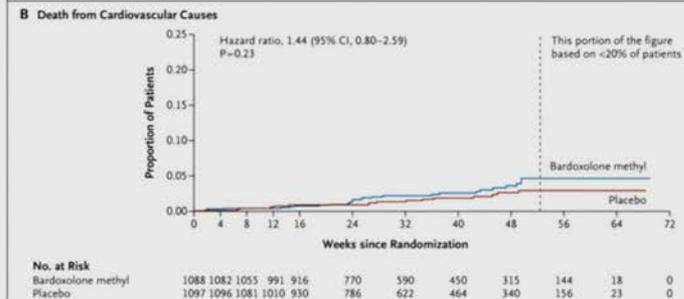
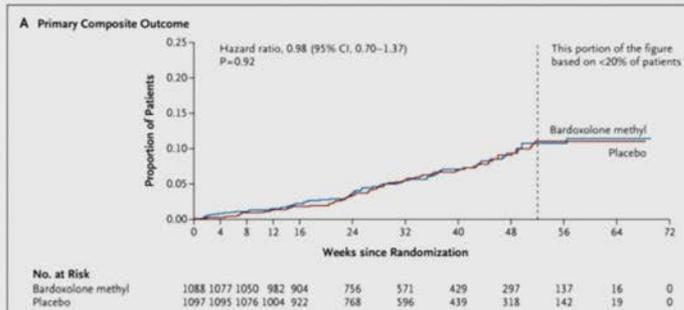
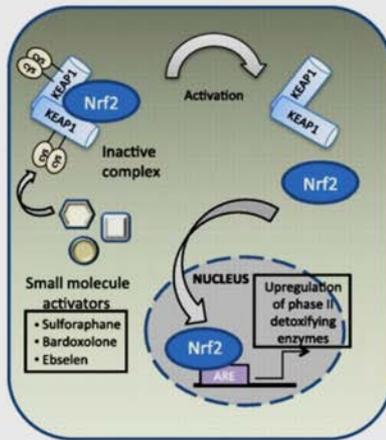
- Genomica
- Epigenomica
- Trascrittosomica
- Proteomica
- Metabolomica



# RICERCA PRE-CLINICA

RISULTATI PROMETTENTI IN VITRO ED IN VIVO NON SEMPRE CONFERMATI NELL'UOMO

## Anti-oxidant Bardoxolone not Beneficial in Diabetic Nephropathy



de Zeeuw D et al. N Engl J Med 2013;369:2492-2503.

de Zeeuw D et al. N Engl J Med 2013;369:2492-2503.

	1088	1082	1055	991	916	770	590	450	315	144	18	0
Bardoxolone methyl	1088	1082	1055	991	916	770	590	450	315	144	18	0
Placebo	1097	1096	1081	1010	930	786	622	464	340	156	23	0

# LIMITI RICERCA PRE-CLINICA



## MODELLO ANIMALE

- Diversità uomo – topo
- Animali gravemente scompensati senza altre terapie



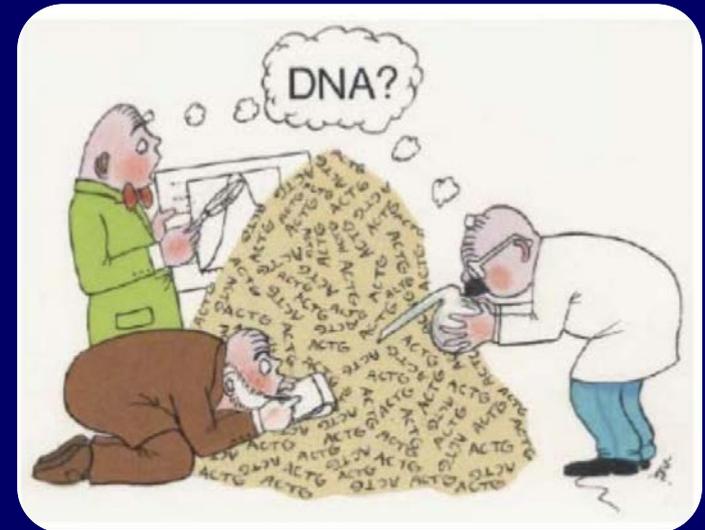
## UNIVERSITA' – AZIENDE

- Università: meccanismi, fisiopatologia,
- Aziende: farmaco-cinetica/dinamica, applicabilità, risvolti economici

# LIMITI RICERCA PRE-CLINICA

## I RISULTATI

- Risultati negativi non pubblicati
- Limitata riproducibilità
  - Elevata variabilità
  - Validazione reagenti (anticorpi)
- Omica Data
  - Enormi dataset
  - Riproducibilità e interpretazione
  - Azione
    - Standardizzazione – validazione
    - Strumenti di analisi, integrazione
    - Condivisione



# FONDI

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
PRIN	126	134	137	137	131	82	110	96	106	100	75	39			92
FIRB				155	137	85	39	50	90	92	8	32	30		



## RICERCA APPLICATA-TRANSLAZIONALE *CRISPR CAS9*

- Scoperta del secolo
- Studio dei meccanismi con cui i batteri si difendono dai virus

## VALUAZIONE PERFORMANCE

### *Indici Bibliometrici*

- $n^{\circ}$  pubblicazioni
- $n^{\circ}$  citazioni

# IL LUNGO VIAGGIO ...



RICERCA DI BASE

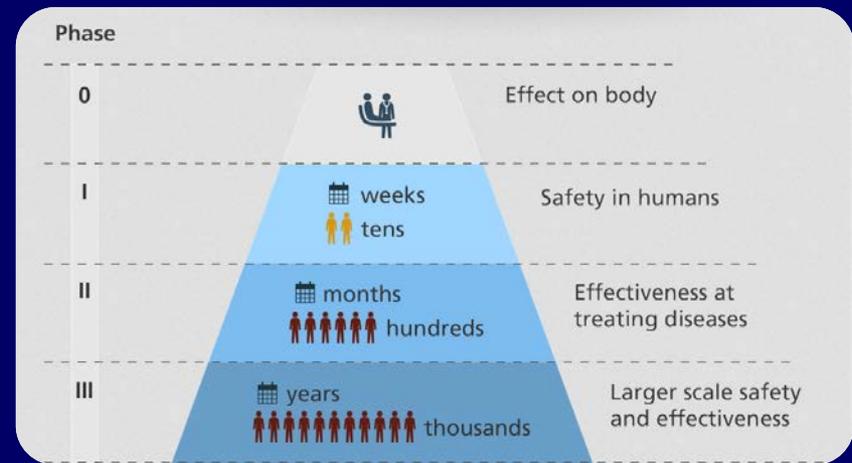
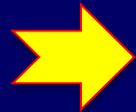
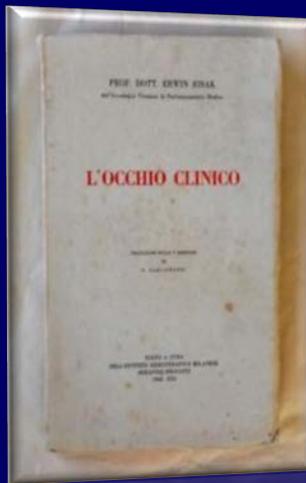


RICERCA CLINICA



APPLICAZIONE  
nella PRATICA  
CLINICA

# TRIAL CLINICI



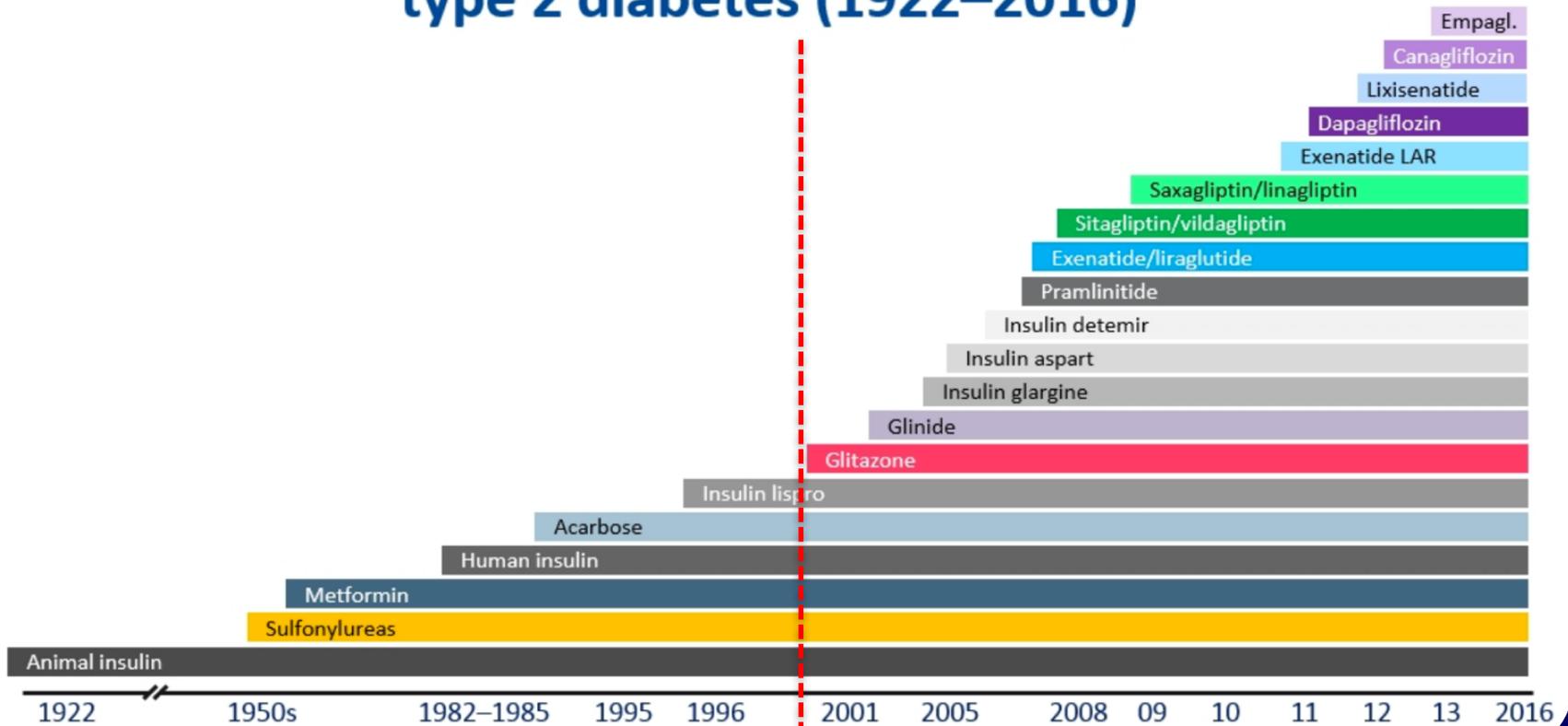
**VALUTAZIONE SOGGETTIVA**

**EVIDENZA SCIENTIFICA**

- Gold standard: efficacia e sicurezza

# TRIALS CLINICI

## Development of antidiabetic therapies for type 2 diabetes (1922–2016)



1922 // 1950s 1982–1985 1995 1996 2001 2005 2008 09 10 11 12 13 2016

1922 // 1950s 1982–1985 1995 1996 2001 2002 2008 08 10 11 13 2016

Animal insulin  
Sulfonylureas  
Metformin  
Human insulin  
Acarbose  
Insulin lispro  
Glinide  
Glitazone  
Insulin glargine  
Insulin aspart  
Pramlintide  
Exenatide/liraglutide  
Sitagliptin/vildagliptin  
Saxagliptin/linagliptin  
Exenatide LAR  
Dapagliflozin  
Lixisenatide  
Canagliflozin  
Empagl.

# LIMITI TRIAL CLINICI

- Aumento classi disponibili
- Aumento combinazioni possibili
- Impossibile confronto in RCT

Treatments	n = 7
Doublets	21
Triplets	35
Quadruplets	35

# OSTACOLI - TRIAL CLINICI

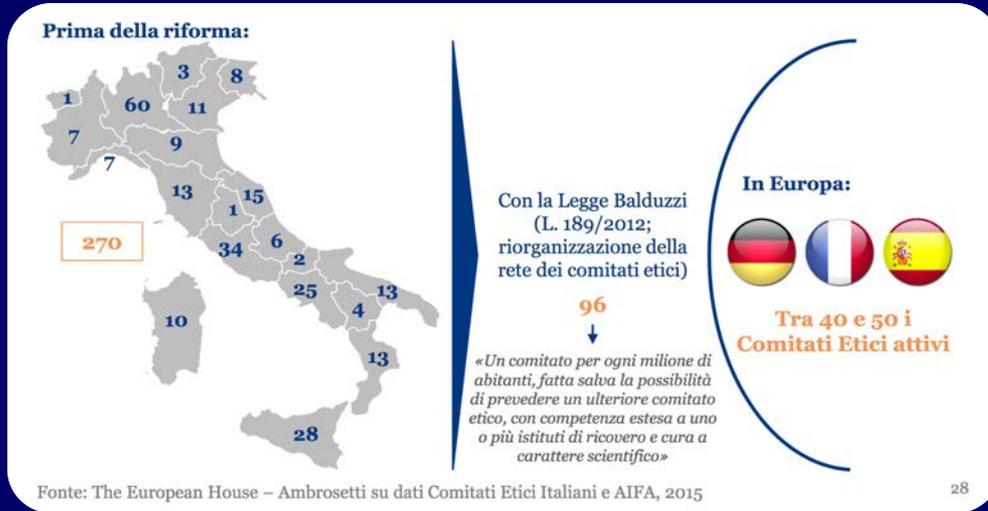
- Costi
- Lavoro burocratico-organizzativo



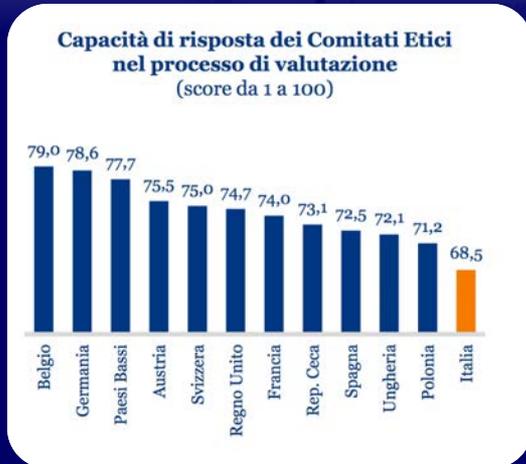
**Tempo medio per l'avvio di studi clinici negli EU-Big 5 (settimane), 2014**



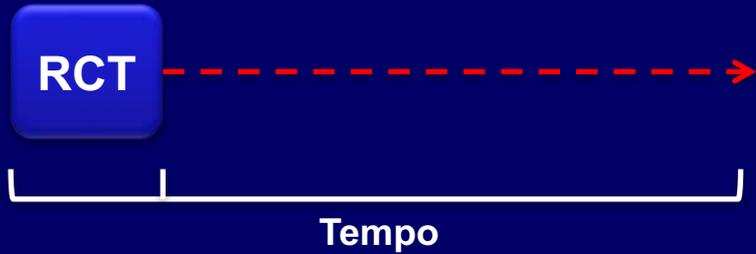
# COMITATI ETICI



- Numerosità: da 270 a 96
- Costosi
- Lenti



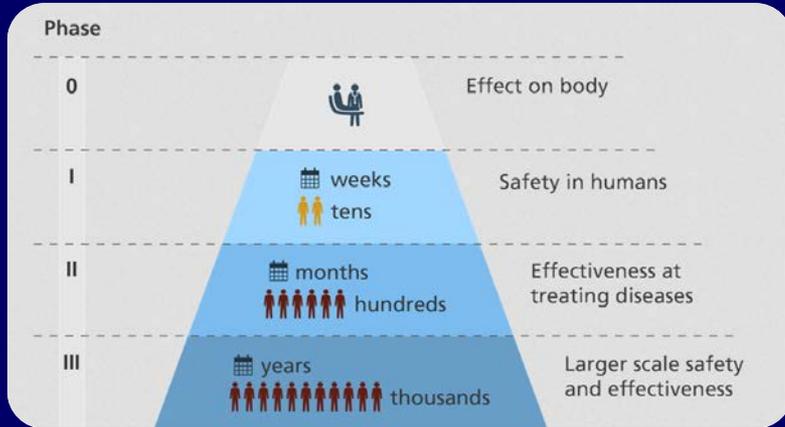
# LIMITI TRIAL CLINICI



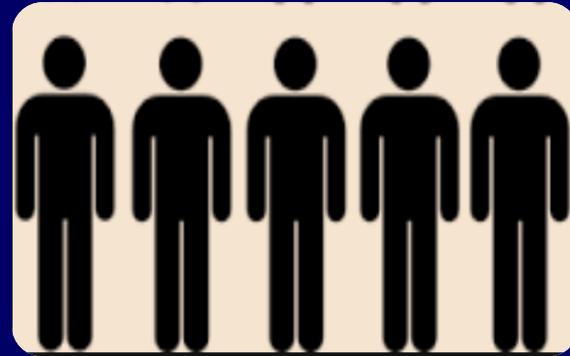
- Efficacia e sicurezza a lungo termine
- Il valore aggiunto del farmaco
- Farmaco-economia
  - Payers: Innovazione - Sostenibilità



# TRIAL CLINICI



OMOGENEITA'

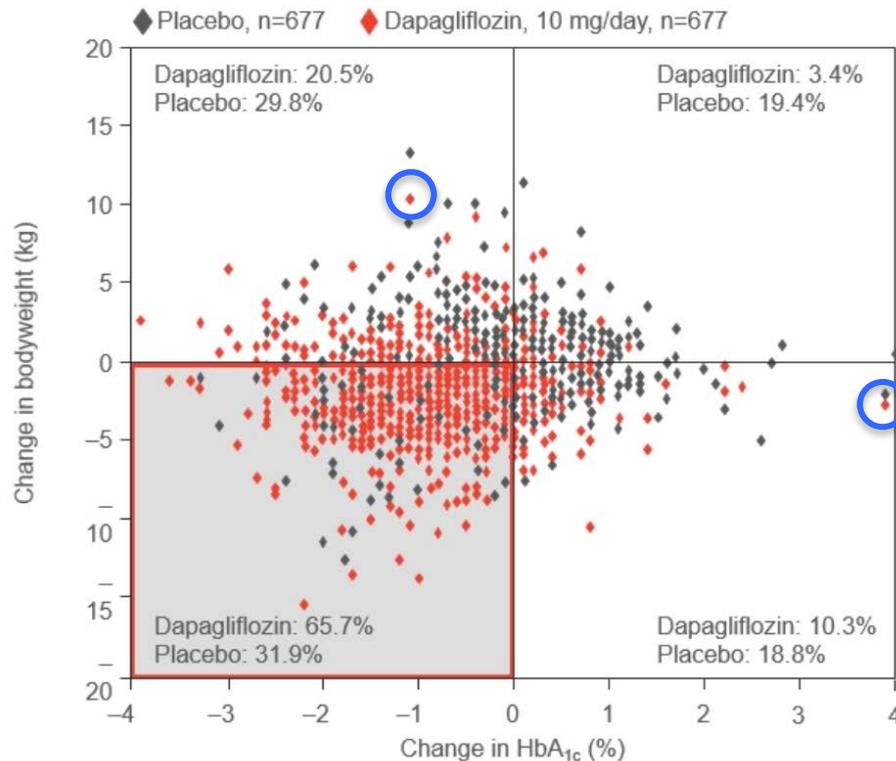


Responders

Non-Responders

# TRIAL CLINICI

**Example of variability in response to treatment:**  
Change in HbA<sub>1c</sub> (%) and weight (kg); pooled data from dapagliflozin RCTs



ETEROGENEITA'  
DI RISPOSTA

Dapagliflozin is not indicated for weight loss. Weight change was a secondary endpoint in clinical trials.

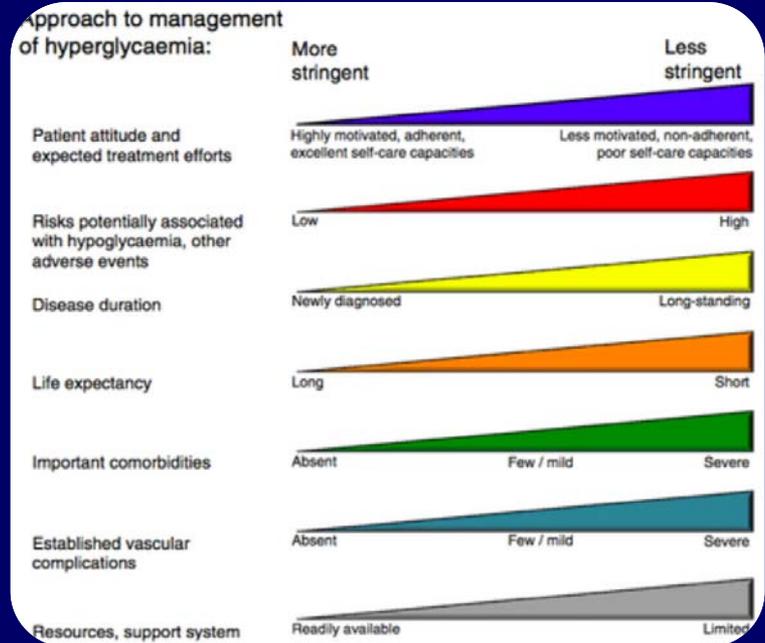
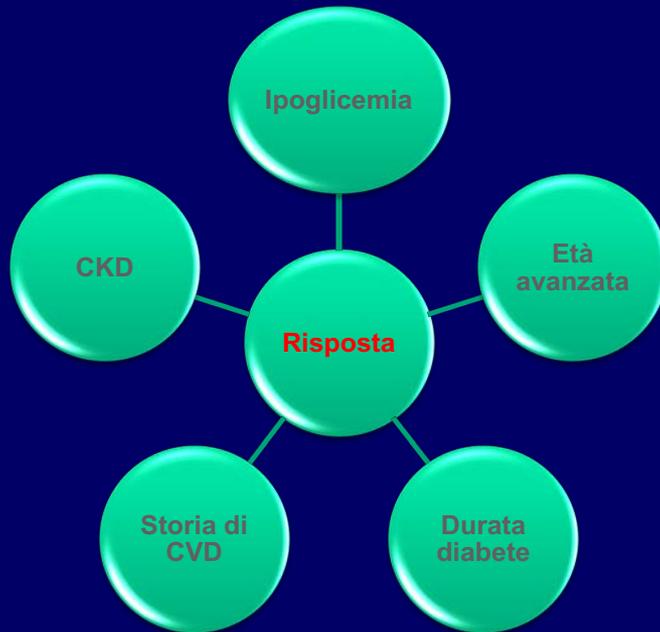
RCT= randomised controlled trial.

Hardy E et al (2012) Presented at: 72nd Scientific Sessions of the American Diabetes Association (Poster 987-P) Philadelphia, PA, USA

Hardy E et al (2012) Presented at: 72nd Scientific Sessions of the American Diabetes Association (Poster 987-P) Philadelphia, PA, USA  
RCT= randomised controlled trial  
Weight change was a secondary endpoint in clinical trials

# TRIAL CLINICI: I SOTTOGRUPPI

Study	Microvasc	CVD	Mortality
ACCORD	↓	↔	↑
ADVANCE	↓	↔	↔
VADT	↓	↔	↔



# MEDICINA DI PRECISIONE

Un approccio emergente al trattamento ed alla prevenzione delle malattie che tiene conto della variabilità individuale o per sottogruppi



# MEDICINA DI PRECISIONE: *DIABETE VS. ONCOLOGIA*

## Cancer

### Initial Treatment :

- Broad Type
- Histological subtype
- Molecular subtype
- Aggressiveness (metastatic spread)

### Subsequent treatment:

- depends on initial response
- Ineffective treatment discontinued

## Diabetes

- Yes T1/T2
- No
- No
- No
- No
- No

- Diabetologia concentrata sulla terapia
- La terapia guidata dalla gravità dello scompenso metabolico

Stile di vita

1

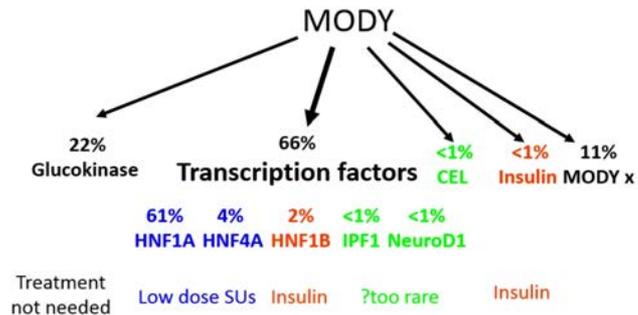
1+1

1+1+1

# TERAPIA GUIDATA DALLA CAUSA

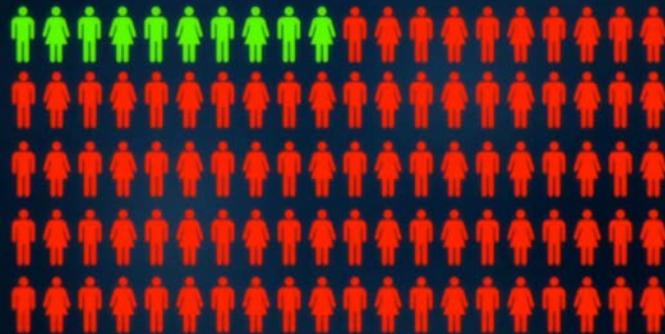
## Precision Diabetes in MODY

Genetic subtype determines clinical picture and treatment response



Anche quando la causa è nota (MODY) e potrebbe guidare la terapia spesso la diagnosi non viene fatta o viene fatta tardivamente

90 - 95% Incorrectly diagnosed  
On the **wrong treatment**



# MEDICINA DI PRECISIONE E DIABETE

- **BIOMARCATORI**

- HbA1c .....

Healthy eating, weight control, increased physical activity, and diabetes education

**Monotherapy**

**Metformin**

Efficacy<sup>1</sup>: high  
 Hypo risk<sup>2</sup>: low risk  
 Weight<sup>3</sup>: neutral / loss  
 Side effects<sup>4</sup>: GI / lactic acidosis  
 Costs<sup>5</sup>: low

*If HbA<sub>1c</sub> target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

**Dual therapy<sup>6</sup>**

	Metformin + Sulfonylurea	Metformin + Thiazolidinedione	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (basal)
Efficacy <sup>1</sup>	high	high	intermediate	intermediate	high	highest
Hypo risk <sup>2</sup>	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight <sup>3</sup>	gain	gain	neutral	loss	loss	gain
Side effects <sup>4</sup>	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs <sup>5</sup>	low	low	high	high	high	variable

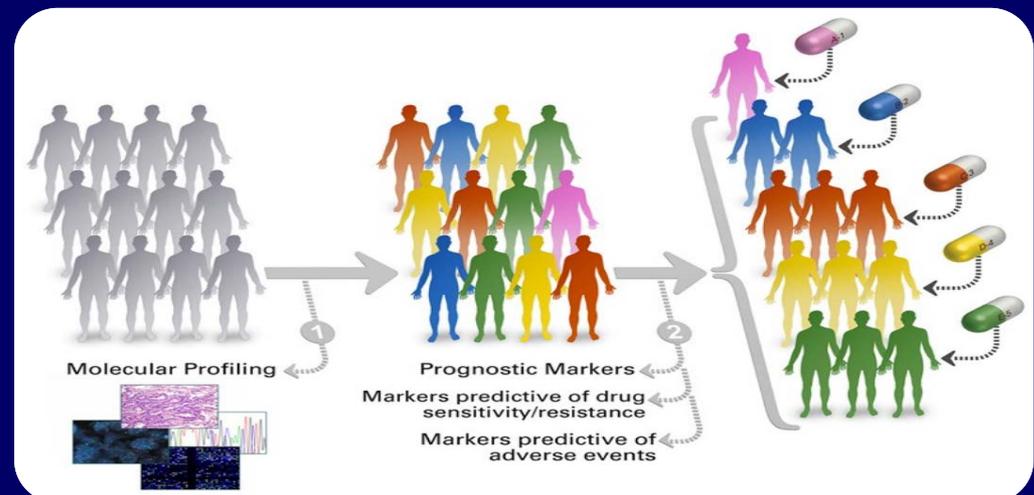
## EFFETTI COLLATERALI E COSTI

- **FENOTIPO CLINICO**

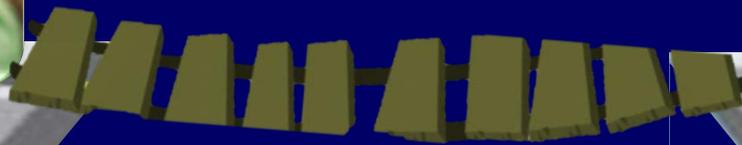
- Sesso, età, BMI, durata malattia, eGFR...

- **PROFILO**

- GENOMICO
- TRANSCRIPTOMICO
- METABOLOMICO
- PROTEOMICO



# BRIDGING THE GAP



# REAL LIFE

EDITORIALI  
META-ANALISI  
CLINICAL TRIALS  
STUDI EPIDEMIOLOGICI



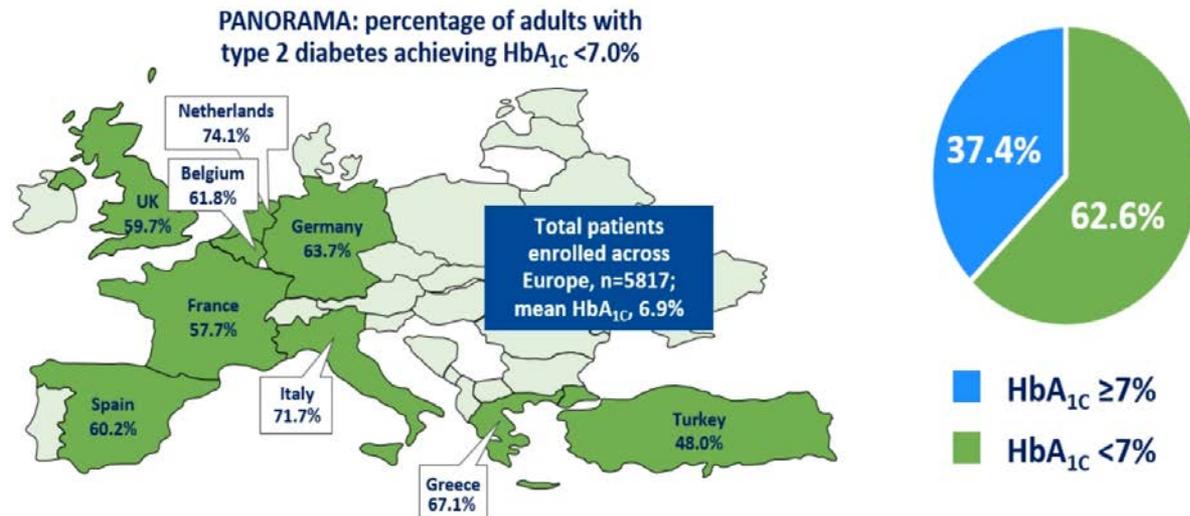
STANDARD ITALIANI PER LA  
CURA DEL DIABETE MELLITO  
VERSIONE AGGIORNATA 2016

# TARGET HbA1C

## ADVANCE ACCORD VADT

Valore target HbA1c <7 vs. <6-6.5

There is a gap between current and optimal management:  
currently, only 60% of patients in Europe achieve HbA<sub>1c</sub> <7.0%



de Pablos-Velasco P, et al. *Clin Endocrinol (Oxf)* 2014;80:47-56.

de Pablos-Velasco P, et al. *Clin Endocrinol (Oxf)* 2014;80:47-56.



# TARGET PRESSORIO

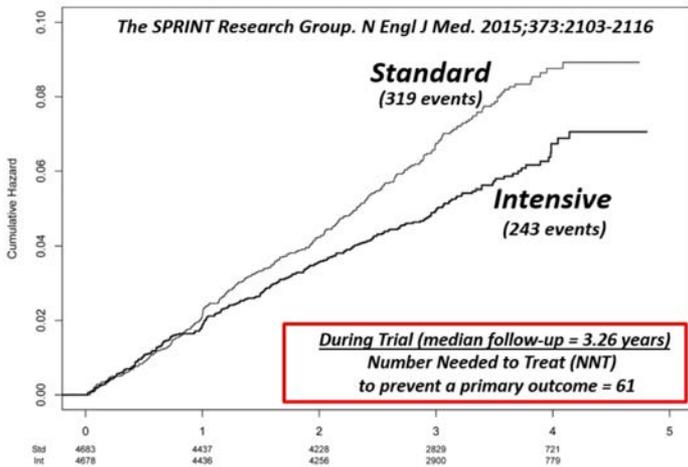
## STUDIO SPRINT

Ps <120 vs <140 mm Hg

### SPRINT Primary Outcome Cumulative Hazard

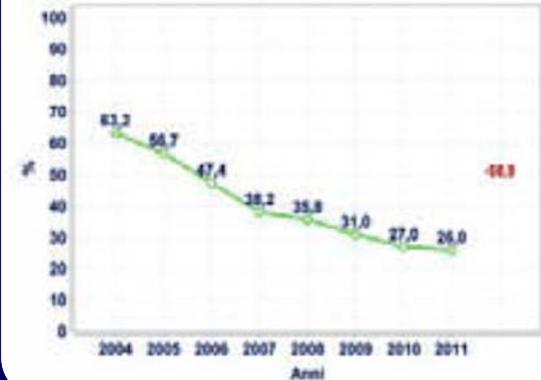
Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

The SPRINT Research Group. N Engl J Med. 2015;373:2103-2116



	Hazard Ratio	P value
<b>Primary Outcome</b>	0.75	<0.001
<b>Components</b>		
All MI	0.83	0.19
Non-MI ACS	1.00	0.99
All Stroke	0.89	0.50
All HF	0.62	0.002
CVD Death	0.57	0.005

### Piemonte/Val d'Aosta



PAO >140/90 senza anti-  
ipertensivi  
Annali AMD 2014

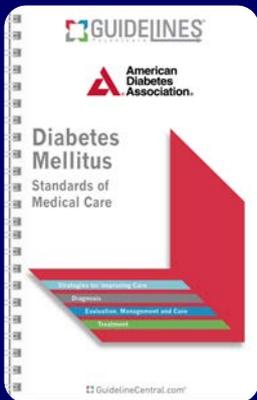
# IL SACRO GRAAL

Ricerca di un target *ideale*,  
*perfetto* nasconde la  
difficoltà a raggiungere  
raggiunge un target  
*ragionevole*



# RUOLO DELLE SOCIETA' SCIENTIFICHE

- Identificazione e superamento delle barriere alla implementazione
  - Utilizzo nei siti di cura: versioni pocket ed online, app di supporto decisionale



Versione pocket



Versione online



App di supporto decisionale



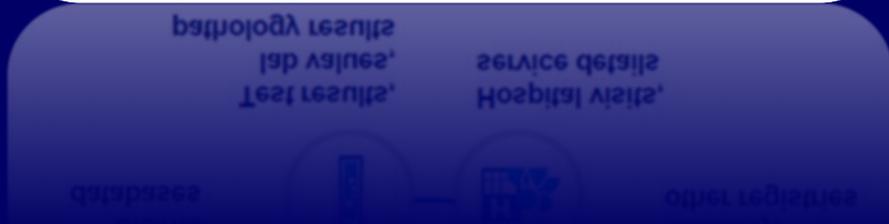
# REAL LIFE

Real Life: sede di implementazione dei risultati ottenuti nei RCT

## *IL MITO DELLA CAVERNA*

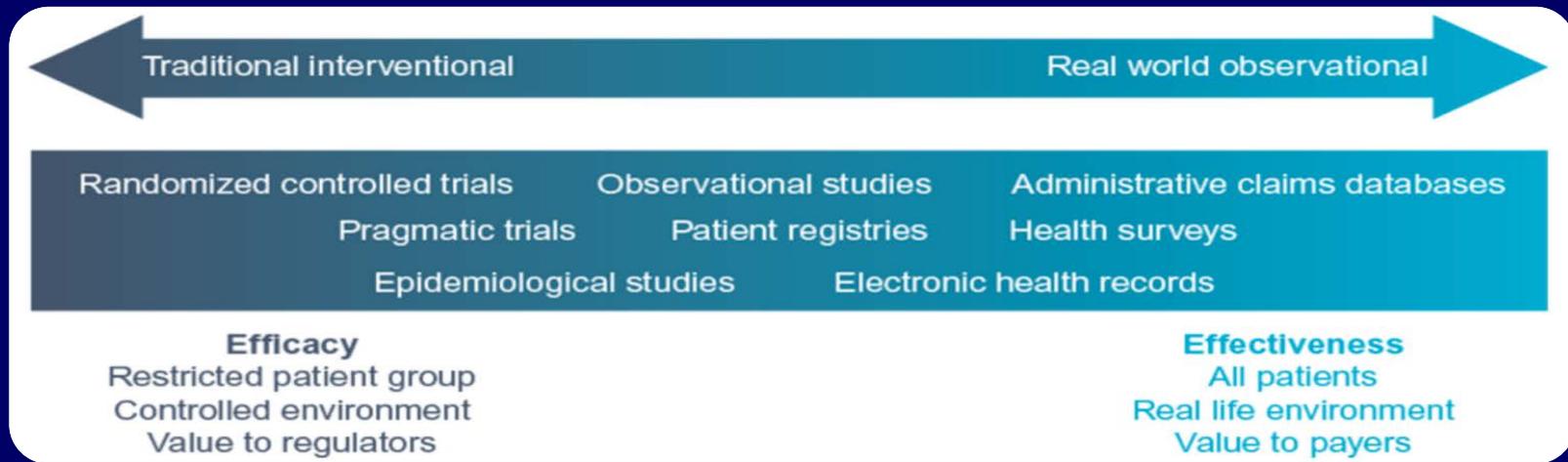


# REAL WORLD DATA



# REAL LIFE

- Risultati dei RCT condotti su popolazioni predefinite e ristrette valutate in un contesto controllato per un limitato lasso di tempo possono non essere rappresentative degli effetti dell'intervento nel mondo reale della pratica clinica
- Miglior utilizzo real world data (RWD) è cruciale per completare le informazioni ottenute negli RCT



# RWE e NUOVI TRIALS

## WHAT DOES REAL WORLD EVIDENCE OFFER IN COMPARISON TO CONVENTIONAL RANDOMISED CONTROLLED TRIALS?

### RCTs

Prospective data collection

Limited segment of the population is eligible for inclusion

Good patient adherence and compliance

Important for demonstrating efficacy and safety for drug licensing

Limited ability to investigate costs



### RWE

Prospective and/or retrospective data collection

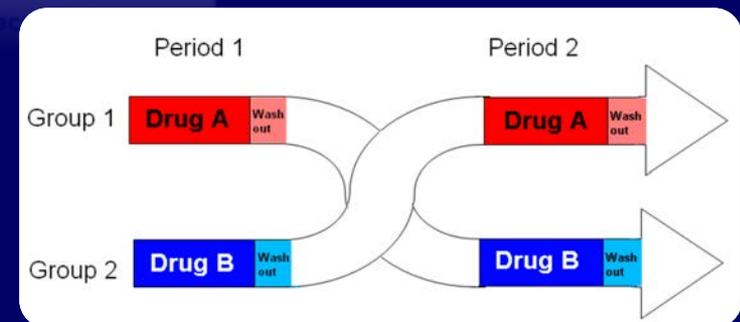
Broader and more representative of the patient population

Real world patient adherence and compliance

Demonstrates the benefits of a drug in everyday clinical practice

Ideal for showing value within local health economy

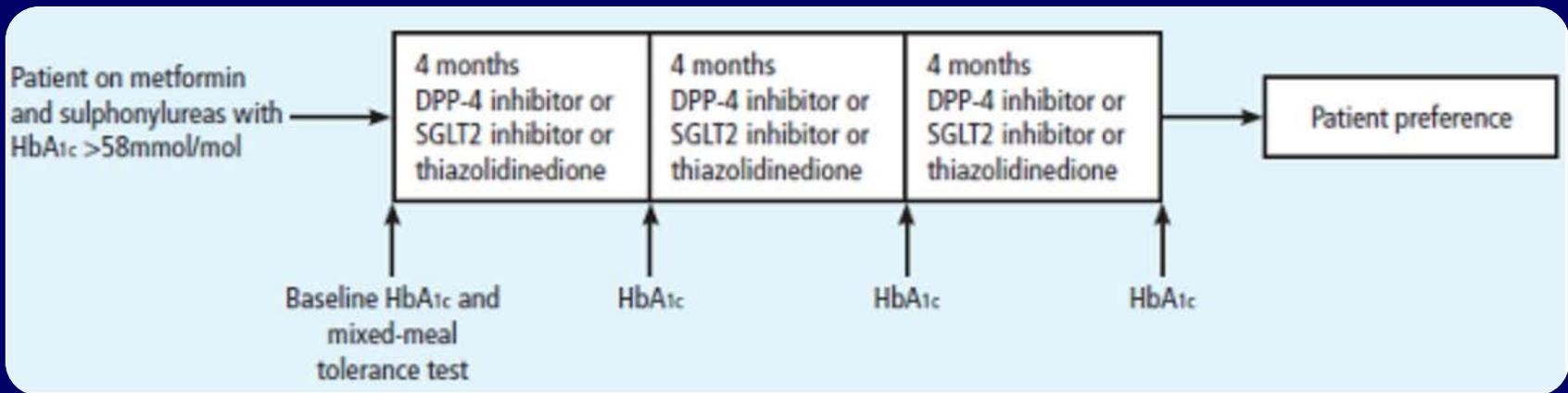
- Trial pragmatici
- N° of 1 trials
- Studi di crossover randomizzati



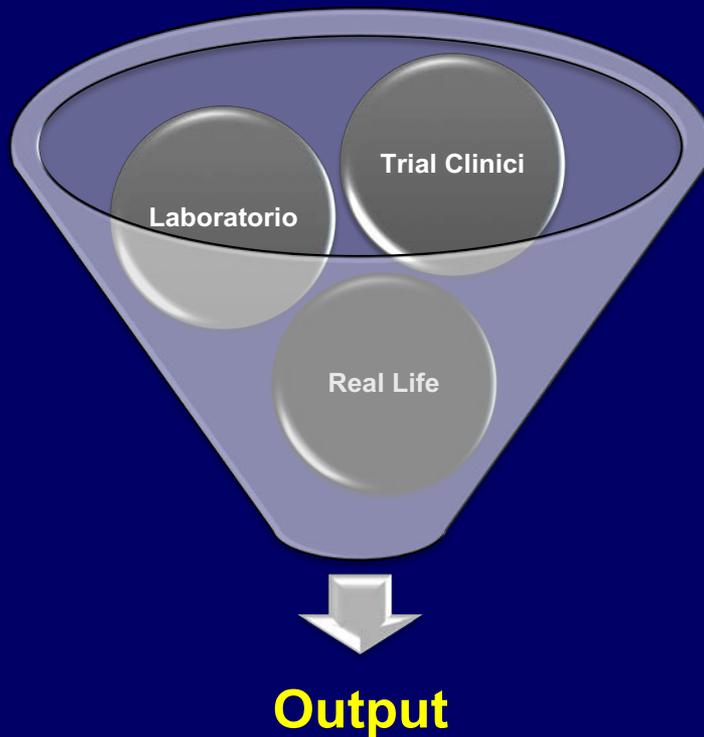
# STUDI CROSS-OVER RANDOMIZZATI

## TRIMASTER TRIAL

- 600 DM2 STRATIFICATI BMI GFR
- Outcome: 1° HbA1c 2° preferenze del paziente

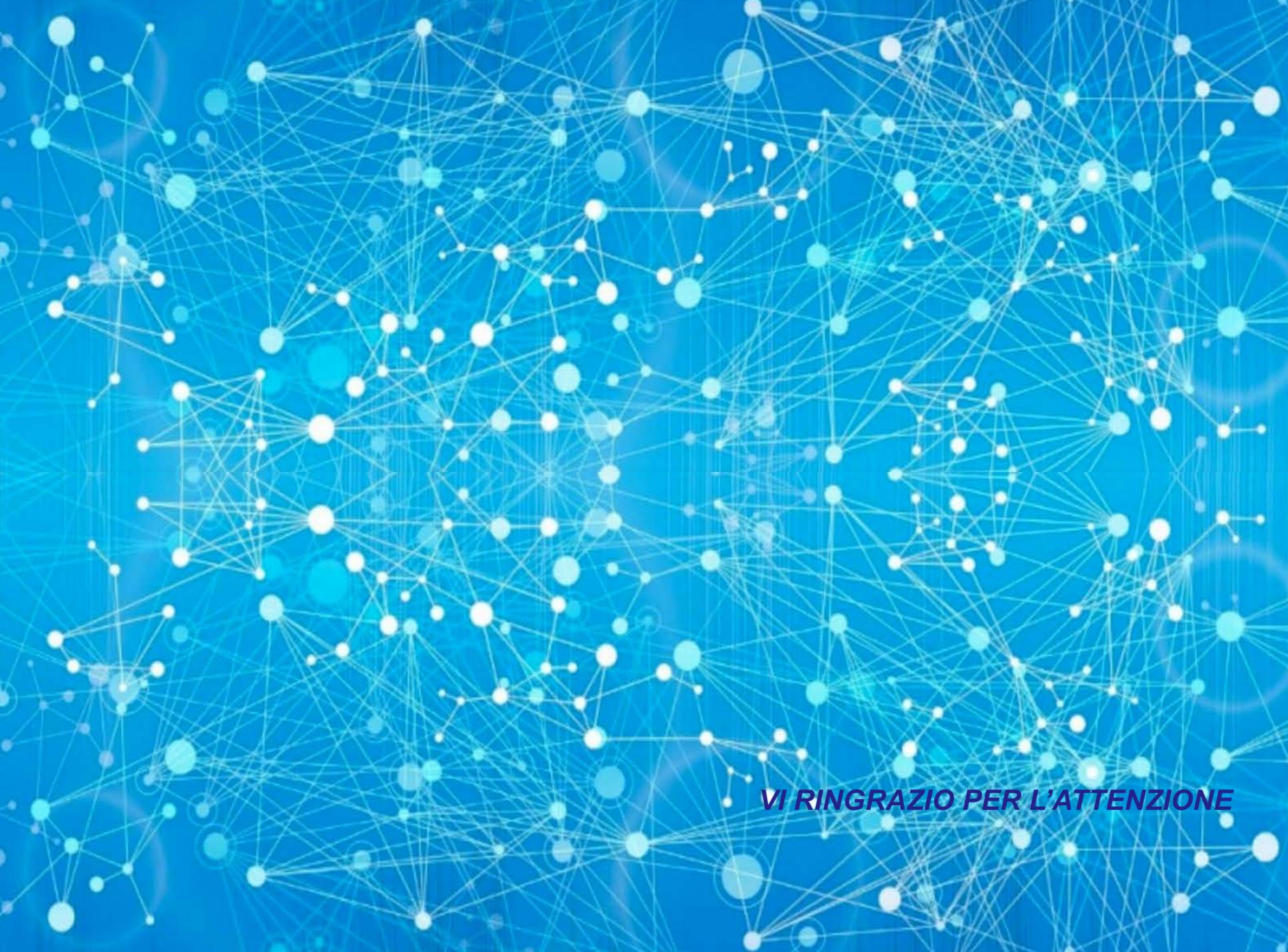


# DALLA SEQUENZA ALL'INSIEME



## BIG DATA

- Digitalizzazione
- Completezza
- Accessibilità
- Integrazione
- Condivisione



***VI RINGRAZIO PER L'ATTENZIONE***