Dall'Evidence-Based Medicine alle valutazioni sull'equivalenza, all'efficacia comparativa

GF Gensini

Genova 14 maggio 2015

1992: nasce la Evidence Based Medicine

Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

2420 JAMA, November 4, 1992—Vol 268, No. 17

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Evidence-Based Medicine
TORONTO

http://ktclearinghouse.ca/cebm/

EBM is the integration of

- **best research evidence with**
- **clinical expertise and**
- **patient values.**

http://ktclearinghouse.ca/cebm/

New evidence from clinical research both

- **invalidates** previously accepted diagnostic tests and treatments and

- **replaces them** with new ones that are
- **more powerful**,
- **more accurate**,
- **more efficacious**, and
- **safer**.

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What kind of evidence?.

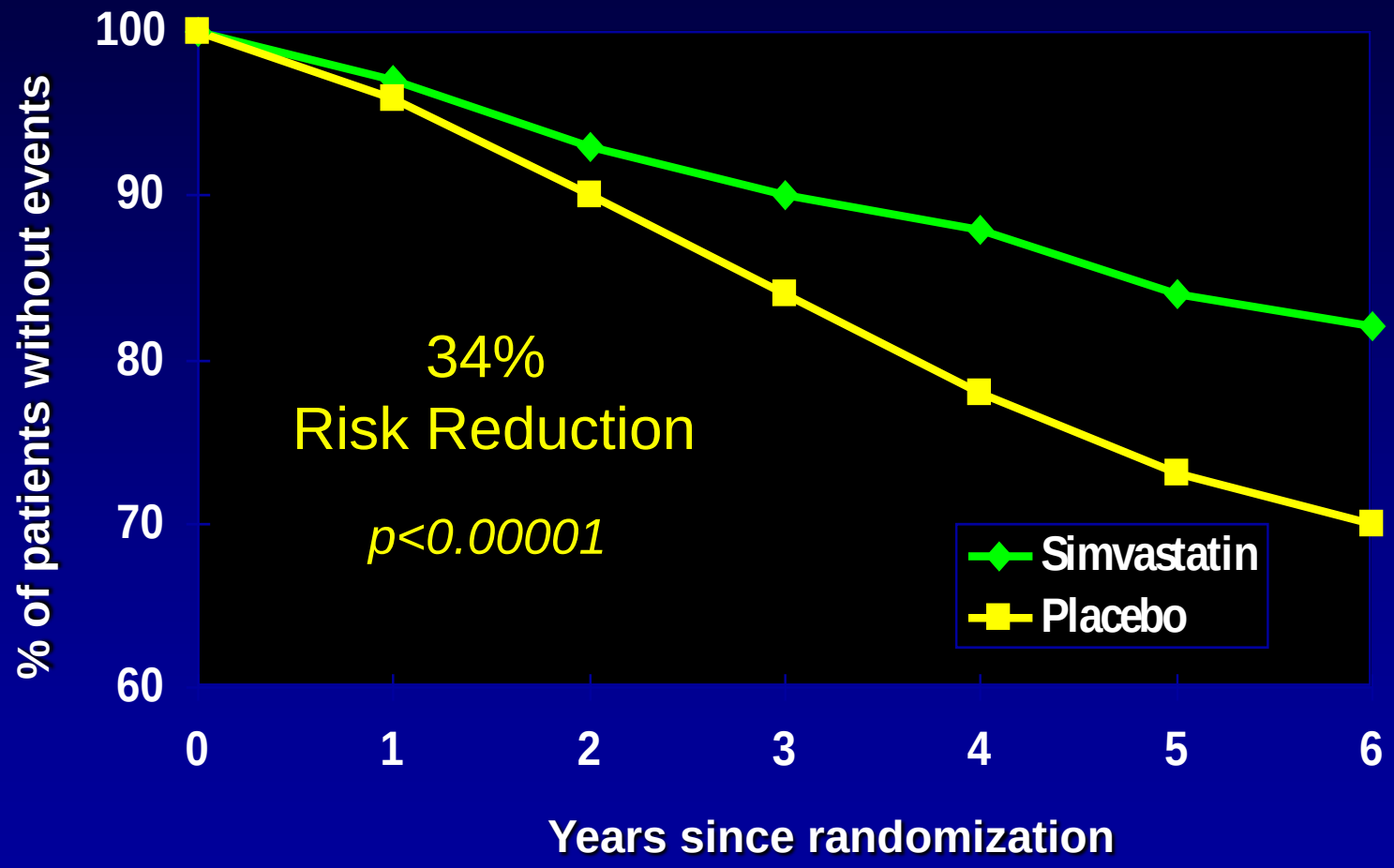
Disease-related evidence

1994: an example of simple Evidence

Scandinavian Simvastatin Survival Study (4S)

The Lancet, Vol 344, November 19, 1994

Coronary Death and Nonfatal MI



Inclusion Criteria: **Prior MI** and/or angina pectoris

The Lancet, Vol 344, November 19, 1994

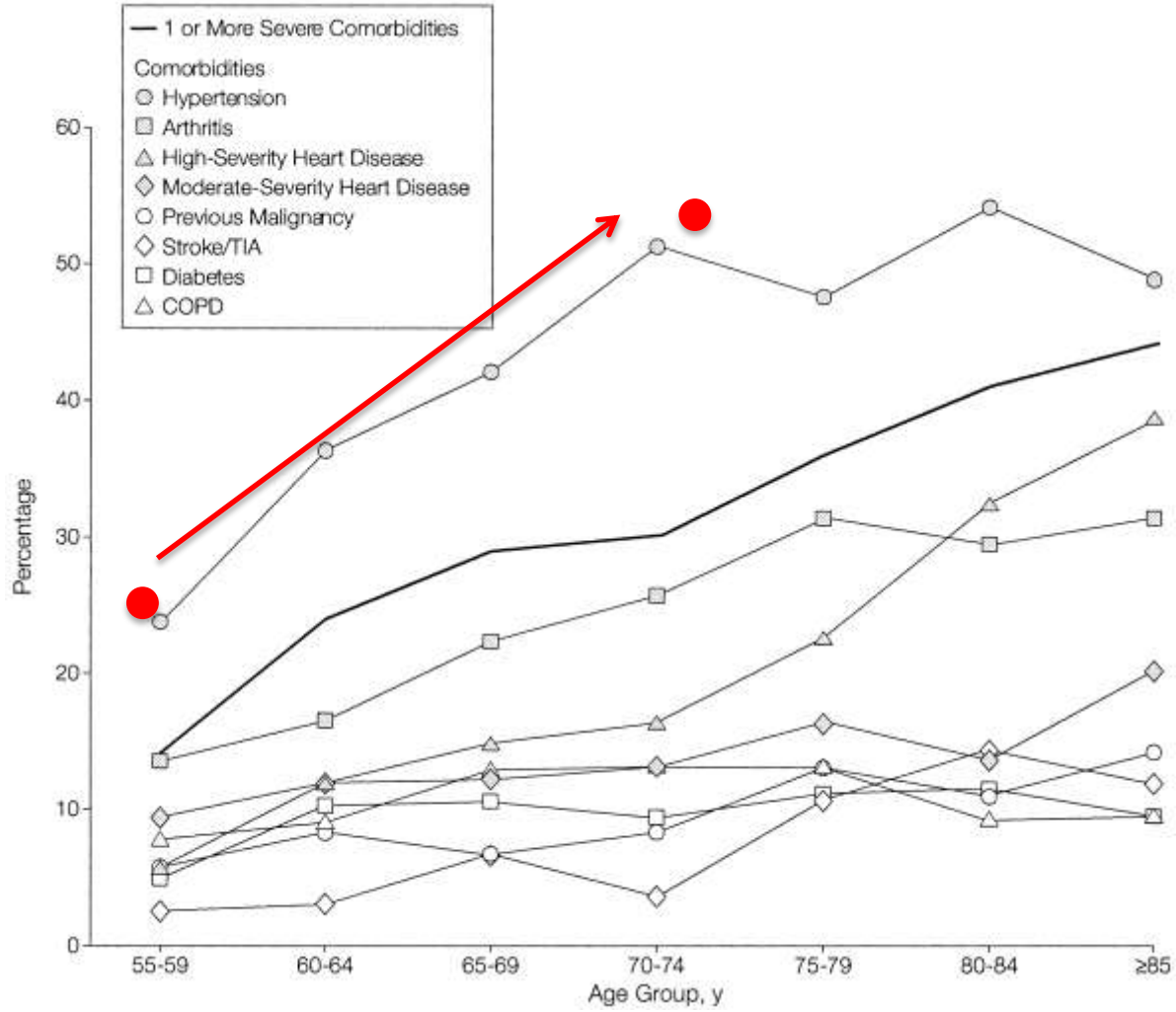
Baseline Characteristics

	Placebo (n=2223)	Simvastatin (n=2221)
Mean age (years)-men	**58.1**	**58.2**
Mean age (years)-women	**60.5**	**60.5**
Angina only	21%	21%
MI only	62%	63%
Both angina and MI	17%	16%
Hypertension	**26%**	**26%**
Smoker	27%	24%
TC (mg/dL)	260	260
LDL (mg/dL)	180	180

The Lancet, Vol 344, November 19, 1994

Importance of co-morbidity

Prevalence and age trends for selected co-morbidities



Holmes 2003

….Changes occurred since 1992

- Ageing
- **Increased comorbidities - multimorbidities**
- These patients are usually **not included** in clinical trials

I “nuovi” pazienti

Sconosciuti

JAMA The Journal of the American Medical Association

Home Current Issue All Issues Online First Specialties & Topics CME Mu

March 21, 2007, Vol 297, No. 11 »

« Previous Article Next Article »

Review | March 21, 2007

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

A Systematic Sampling Review FREE

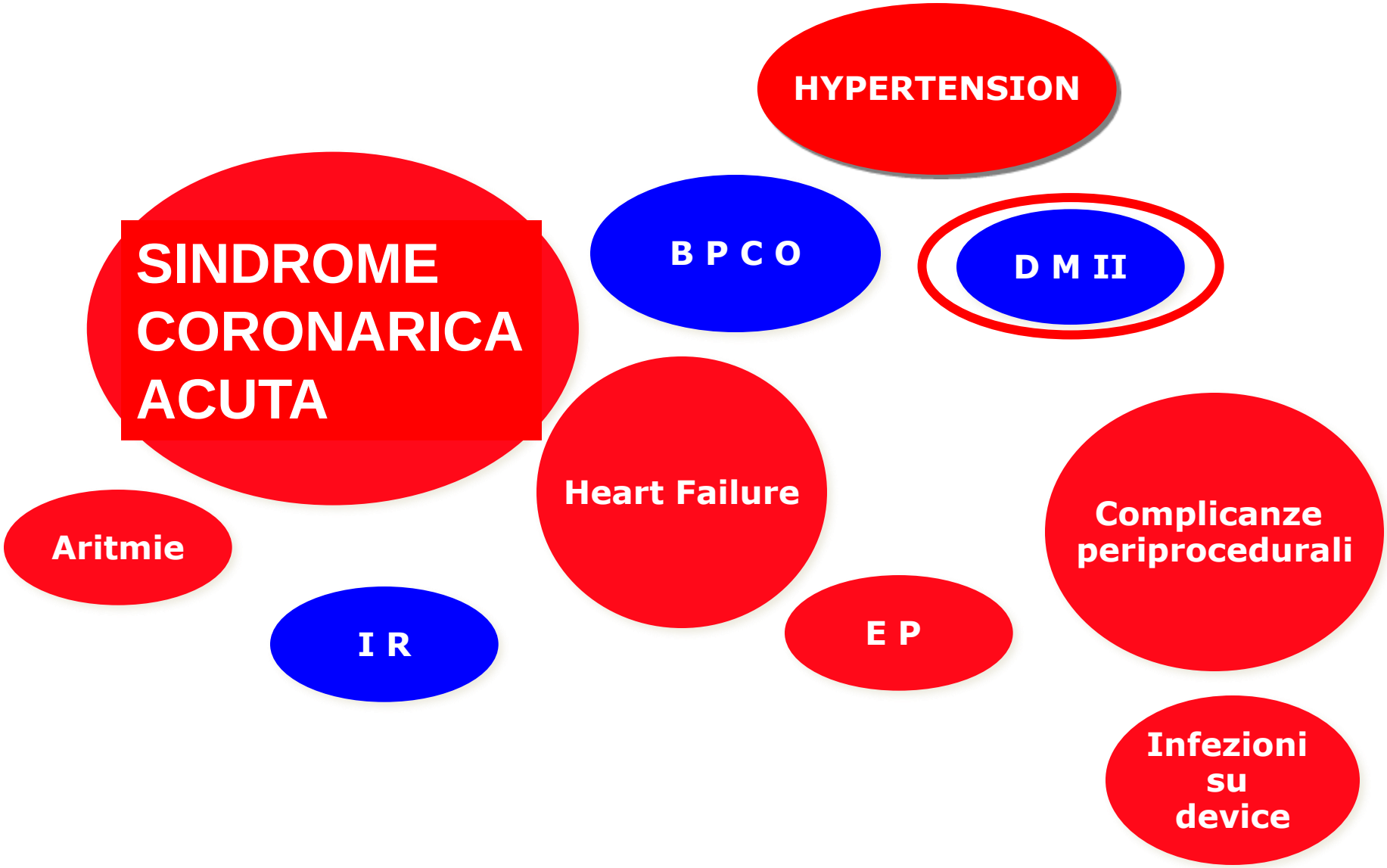
Cause di mancato arruolamento nei trial

- **Età** > 75 (72,1%)
- **Comorbilità (81,3%)**
- **Polifarmacoterapia** (54,1%)

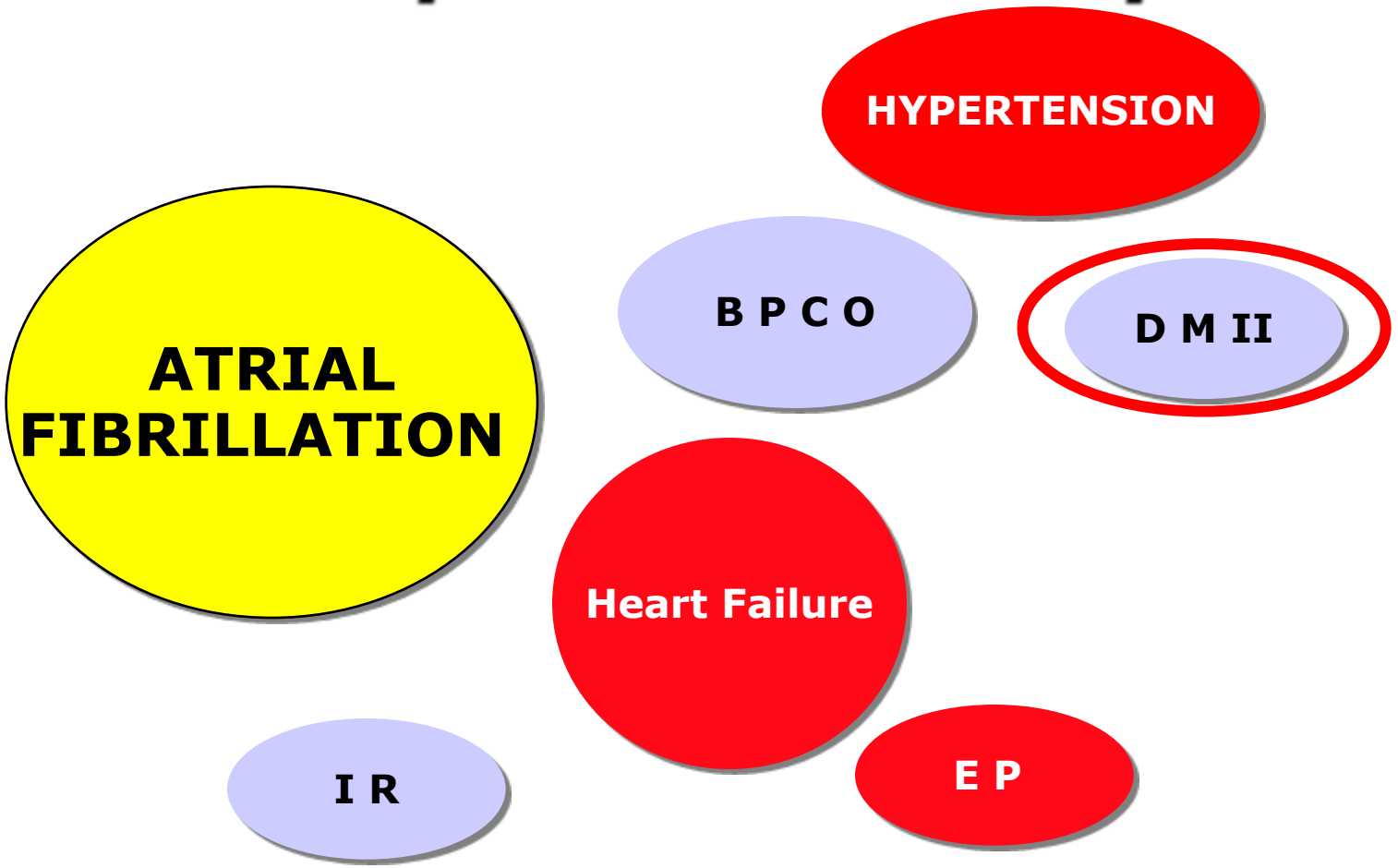
UNIVERSITÀ CATTOLICA del Sacro Cuore

Van Spall HG, 2007

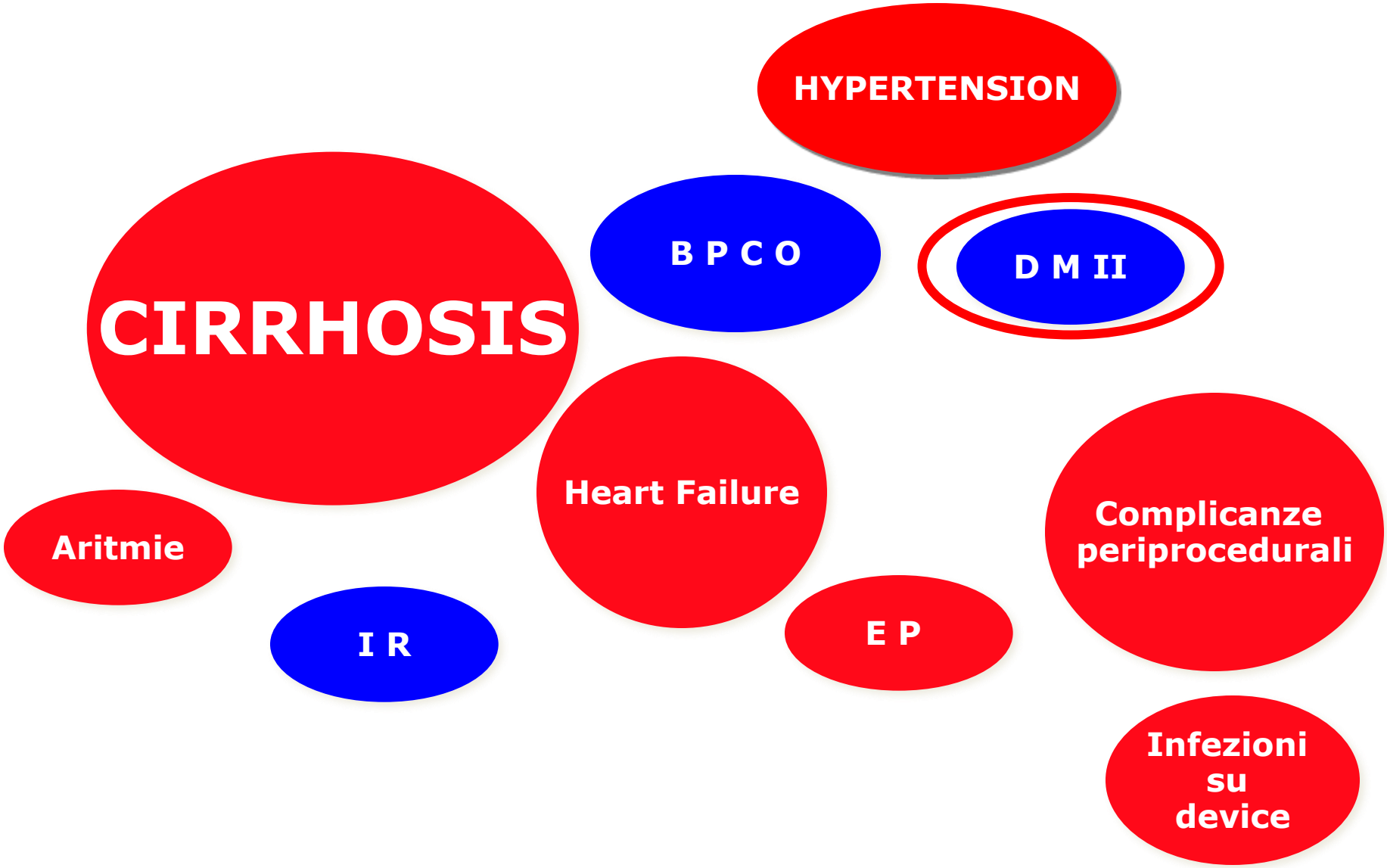
Il fenotipo clinico complesso



Il fenotipo clinico complesso



Il fenotipo clinico complesso



An elementary approach to complexity

Some common measures of comorbidity

- **Disease Count (DC) (!!!?)**
- **Charlson Index (CI)**
- **Index of Co-Existent Diseases ($ICED_{DS}$) ← Index of Disease Severity (IDS)**
- **Geriatric Index of Comorbidity (GIC)**

Etimologia della complessità

- Complesso, complicato e semplice sono termini che vengono tutti dalla stessa radice indoeuropea: plek- (parte, piega, intreccio).Da **plek**- derivano, in latino:
- Il verbo **plicare** = piegare

  Il verbo **plectere** = intrecciare

  Il suffisso **–plex** = parte
- La parola **semplice** = sine plex…

Etimologia della complessità

- Da cum- + plicare deriva: **Complicatus**

Ovvero: complicato (con pieghe)

Può essere “spiegato”

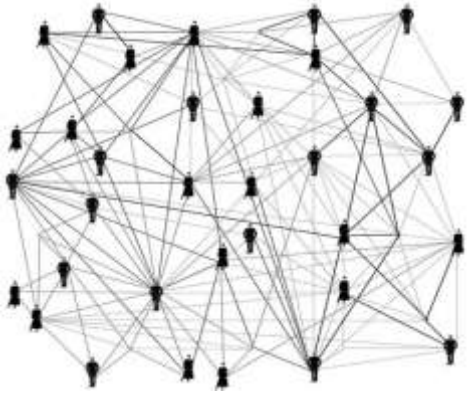
- Da cum- + plectere deriva: **Complexus**
  Ovvero: complesso (con intrecci)
- Non può essere “spiegato”

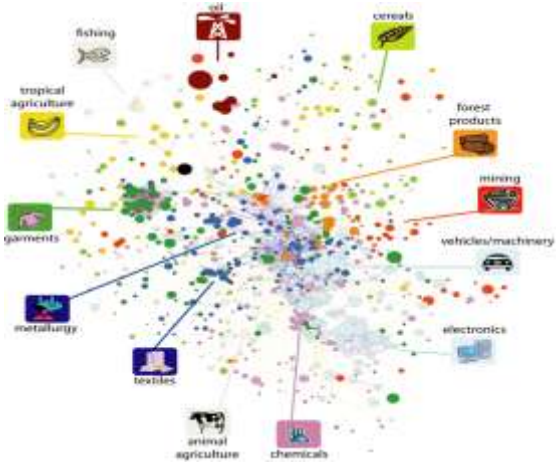
- Da **sine- + -plex** deriva: **Simplex**•
  Ovvero: semplice (senza pieghe)• Né complicato, né complesso

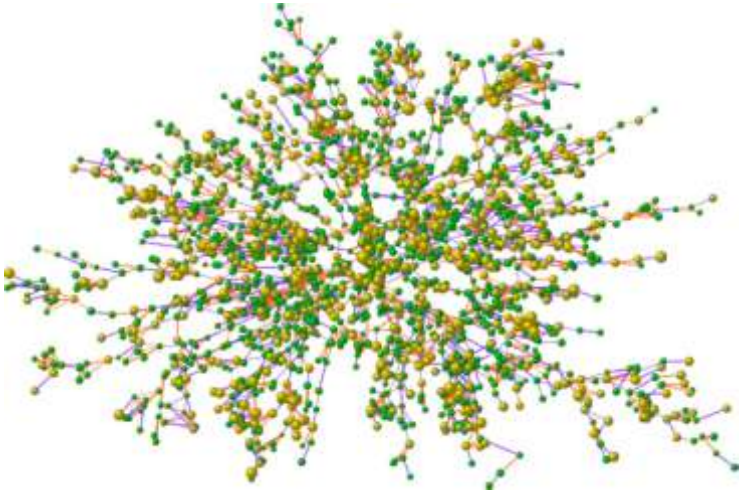
- **The systems perspective is rooted in the assumption that**
- **the forest cannot be explained by studying**
- **the trees individually.**

Complex Systems

Examples of complex systems include **social systems**, **human economies**, **nervous systems**, **cells and living things**, including human beings.







- The explanation **alternative to reductionism** that has received much recent attention, due to systems biology, is the **systems perspective**
- Rather than dividing a complex problem into its component parts**, the systems perspective appreciates the holistic and composite characteristics of a problem** and evaluates the problem with the use of computational and mathematical tools.

I percorsi (diagnostico-terapeutici) sequenziali abituali giungono alla diagnosi di malattia attraverso l'esclusione (guidate dalla *evidence-based medicine)* di altre.

Di fronte alla complessità, al processo di esclusione gerarchica deve essere associata la capacità di includere i diversi elementi, poiché tutti contribuiscono alla genesi del quadro.

An Evolving Scenario

Integrated Care supported by ICT

ICT as enabler of a new model of care

4P medicine

Predictive

Preventive

Participatory

Personalized

An Evolving Scenario

Integrated Care supported by ICT

ICT as enabler of a new model of care

4P medicine

Predictive

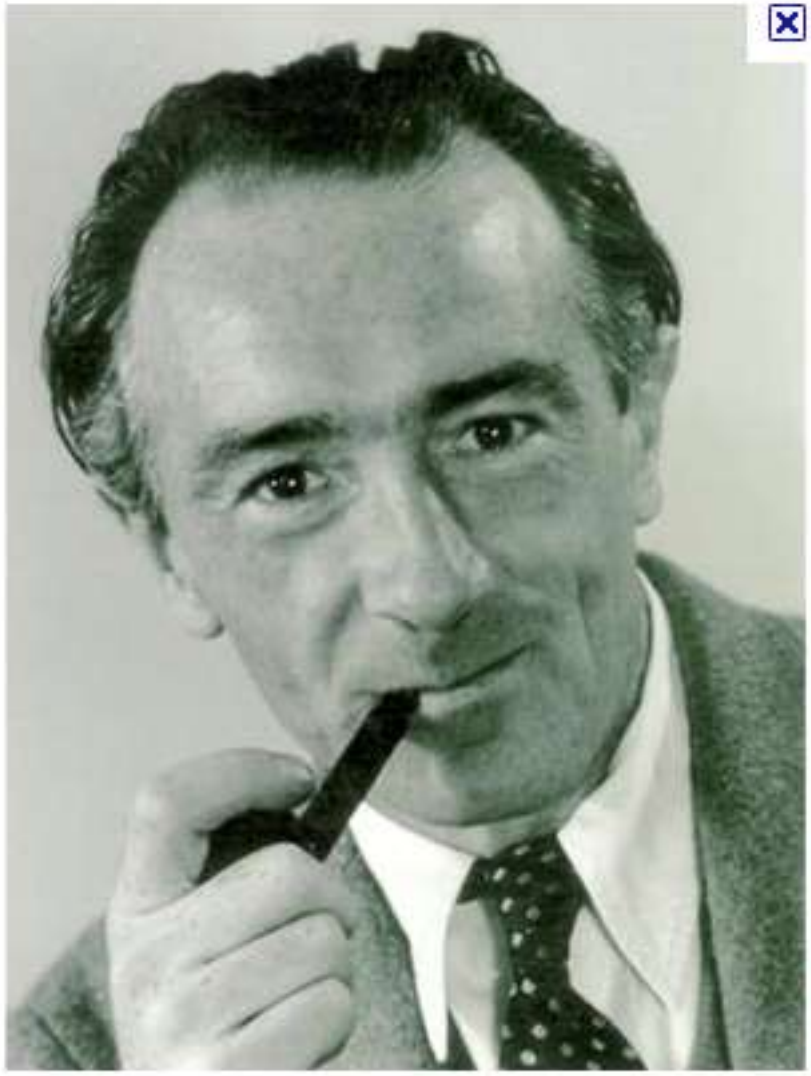
Personalized

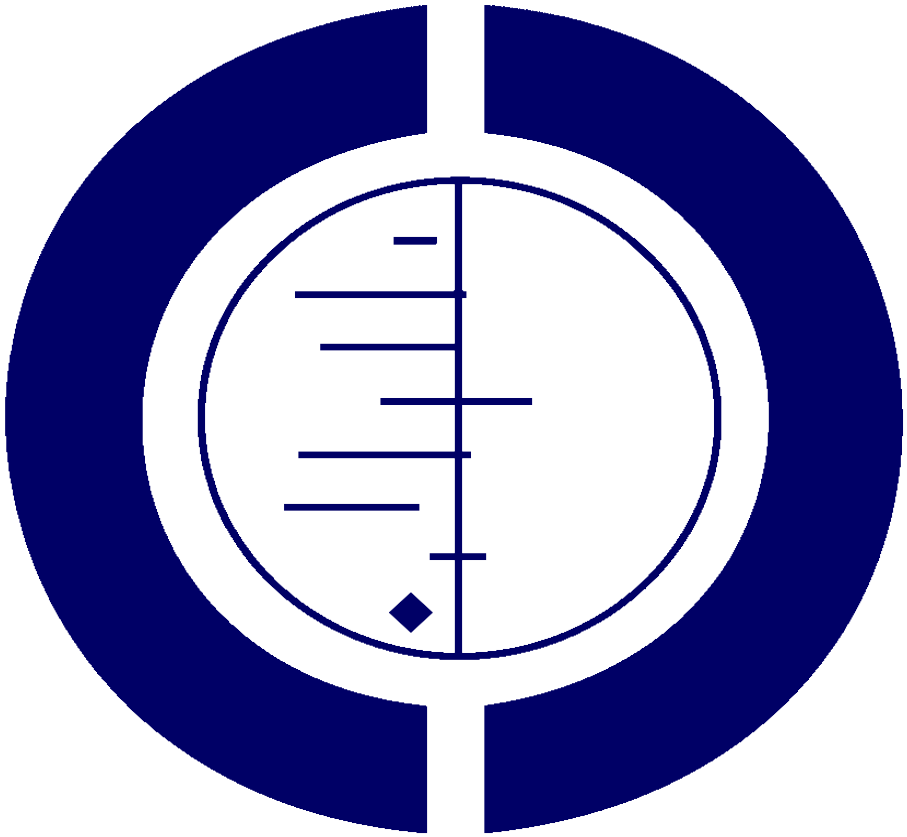
Preventive

Participatory

Efficient patient management

Modulation of disease progress





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"All *effective* treatments should be free"

Archie Cochrane, 1971

1990

2000

Budgeting for cost containment
('Imperativo economico')

Reforms for cost containment through governance of efficacy, efficiency and appropriate use

"All *effective* treatments should be free"
Archie Cochrane, 1971

1990 **2000**

Budgeting for cost containment
('Imperativo economico')

Reforms for cost containment through governance of efficacy, efficiency and appropriate use

"All *effective* treatments should be free"
Archie Cochrane, 1971

"All *cost-effective* treatments should be free"
Alan Williams, 1997

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Sostenibilità

La *sostenibilità* è la caratteristica di un processo o di uno stato che può essere mantenuto ad un certo livello indefinitamente.

Dal punto di vista sociale, il termine indica un *equilibrio* tra il soddisfacimento delle esigenze del presente senza compromettere la possibilità delle future generazioni di sopperire alle proprie (Rapporto Brundtland, 1987).

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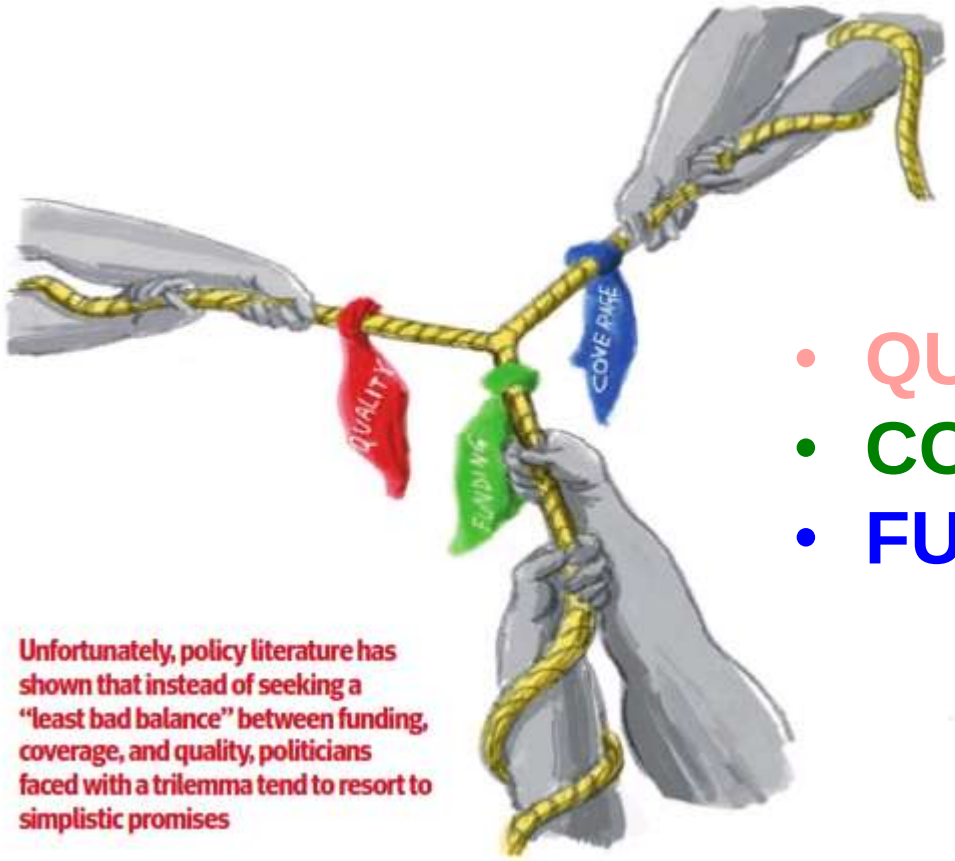


Unfortunately, policy literature has shown that instead of seeking a "least bad balance" between funding, coverage, and quality, politicians faced with a trilemma tend to resort to simplistic promises

- QUALITY
- COVERAGE
- FUNDING

BMJ 2010;340:c1413

La prospettiva britannica

>Ridurre l'eccesso di medicalizzazione e la dipendenza dei pazienti dal sistema di cura

>Smettere di utilizzare terapie non costo-efficaci

>Ridurre i costi amministrativi

>Agire sulle aree di scarsa produttività

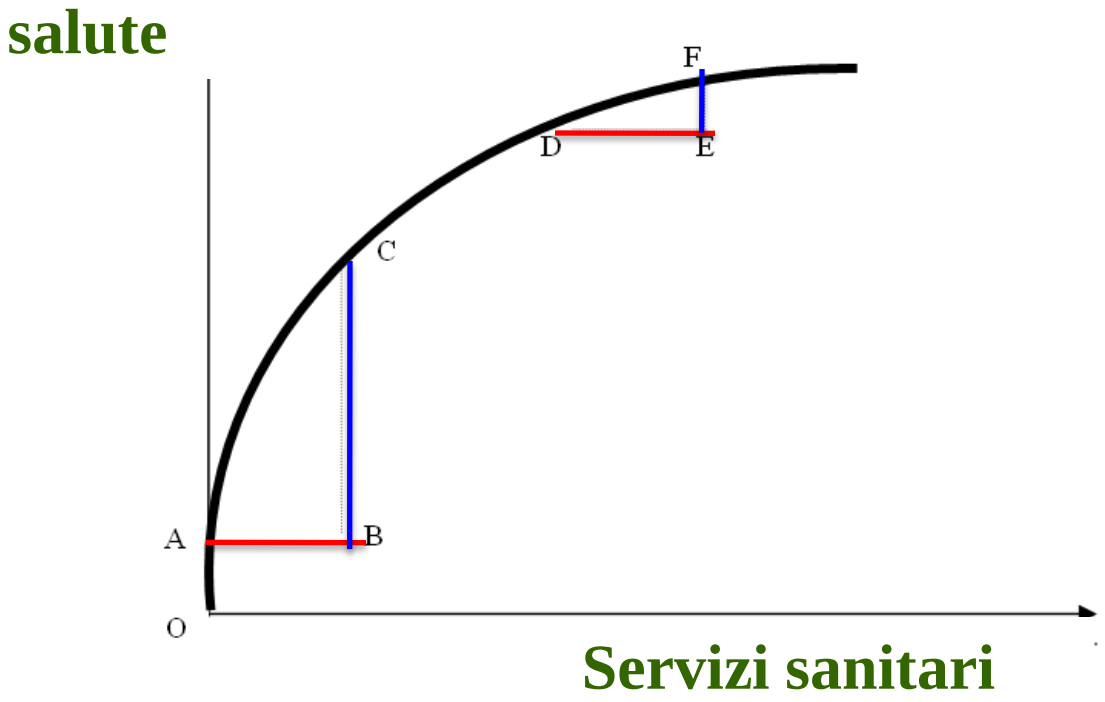
>Concordare gli indicatori

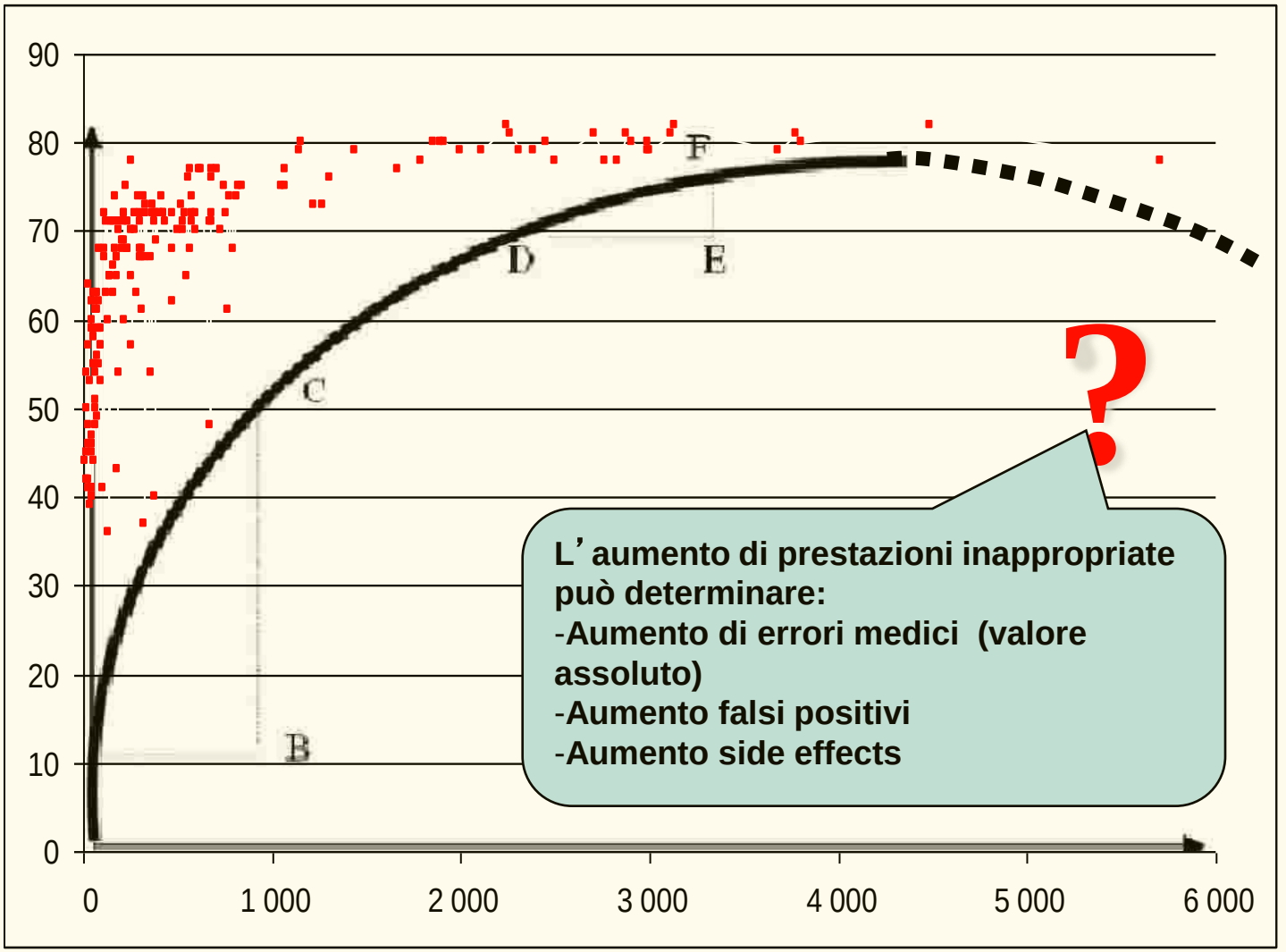
>Coinvolgere gli utenti e migliorarne le conoscenze

>Ottenere migliori contratti con i fornitori

>Management dedicato ai

- **Nel grafico, OA è il livello di salute posseduto in assenza di servizi sanitari.**
- **Le prime dosi di servizi sanitari, AB, producono un aumento di livello di salute, BC, di gran lunga più elevato di quello prodotto dalle dosi successive di servizi (DE produce un incremento di salute pari solo a EF).**

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?
L'aumento di prestazioni inappropriate può determinare:
-Aumento di errori medici (valore assoluto)
-Aumento falsi positivi
-Aumento side effects

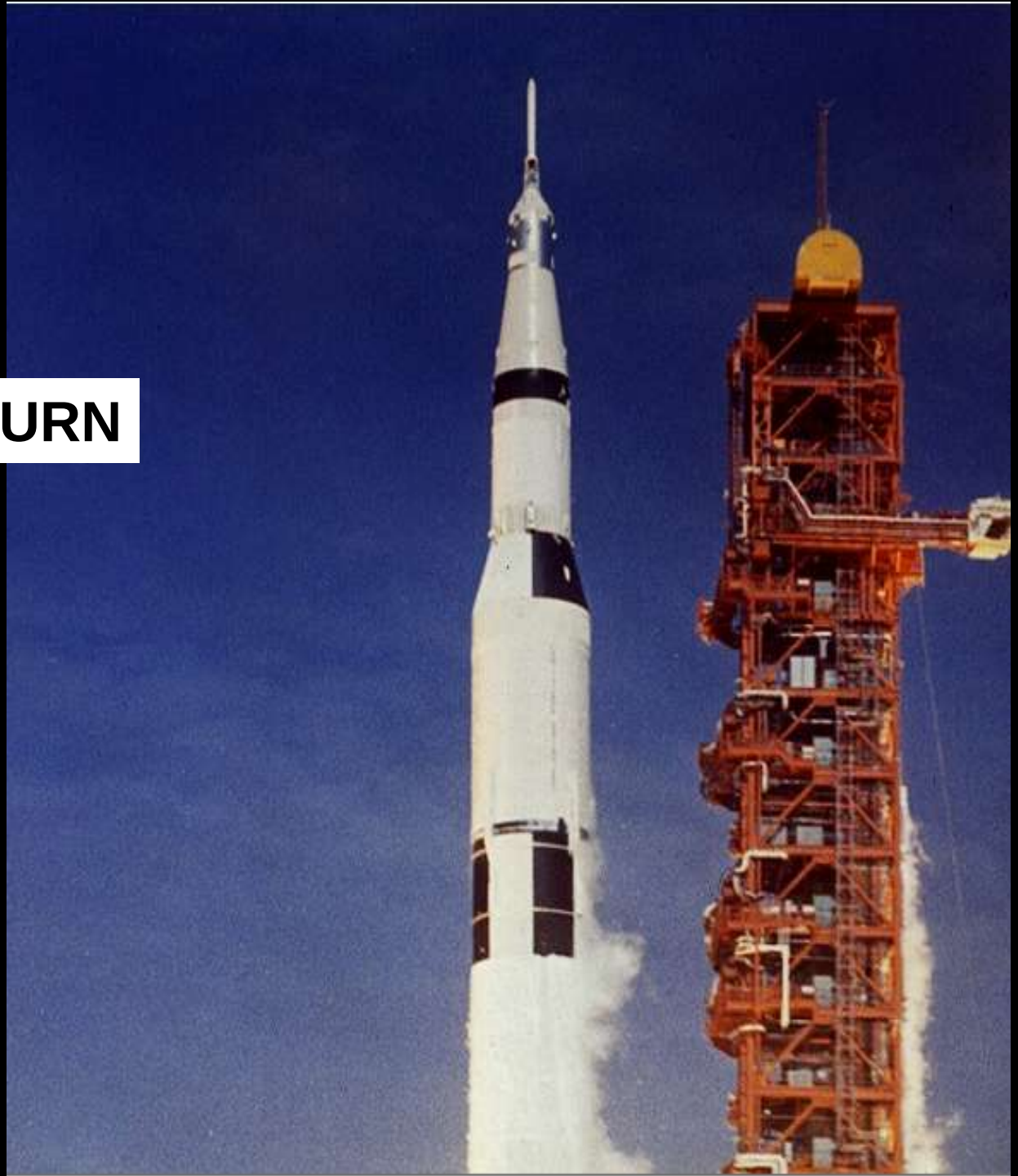
EBM

Health Technology Assessment

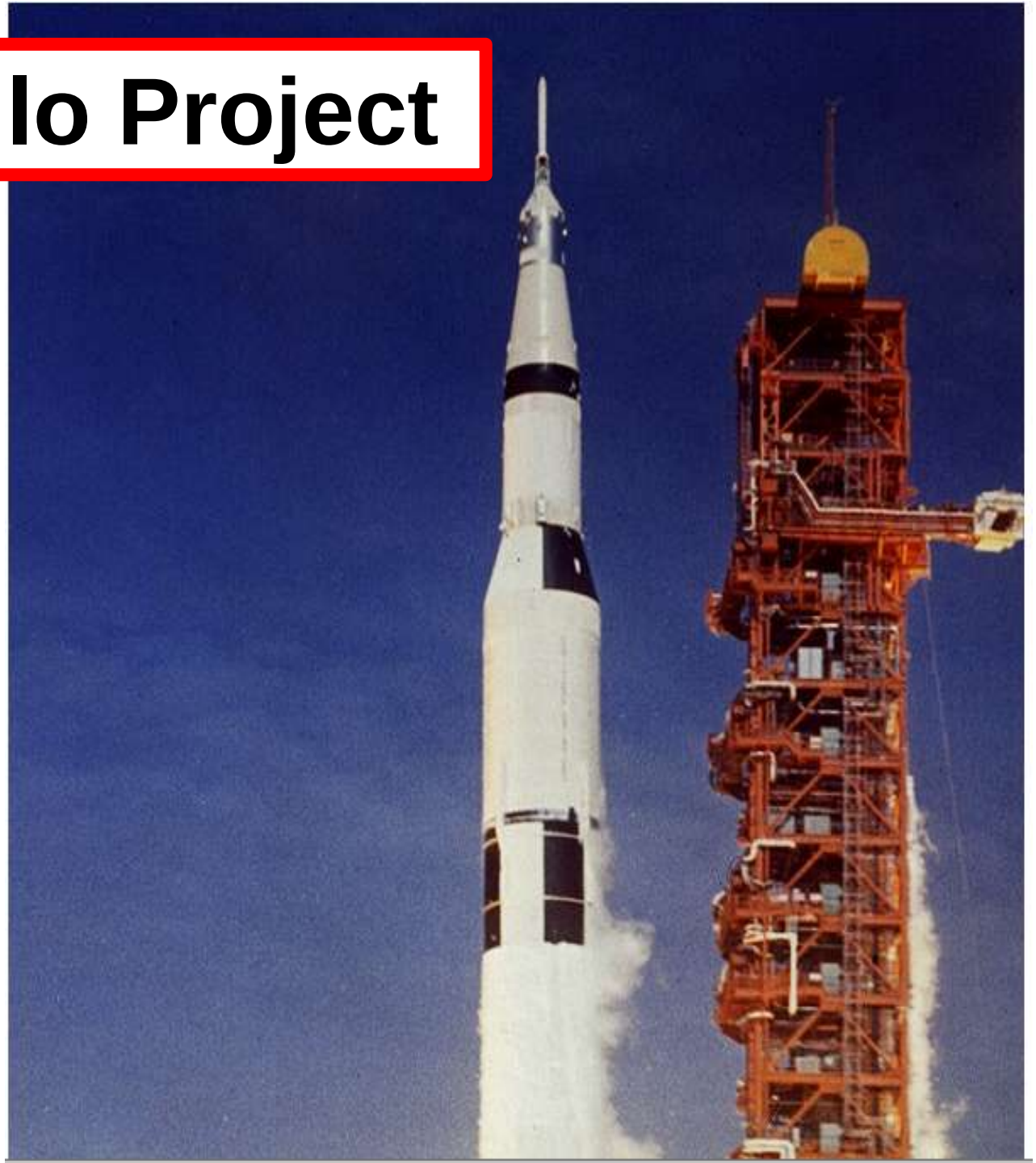
HTA

TA

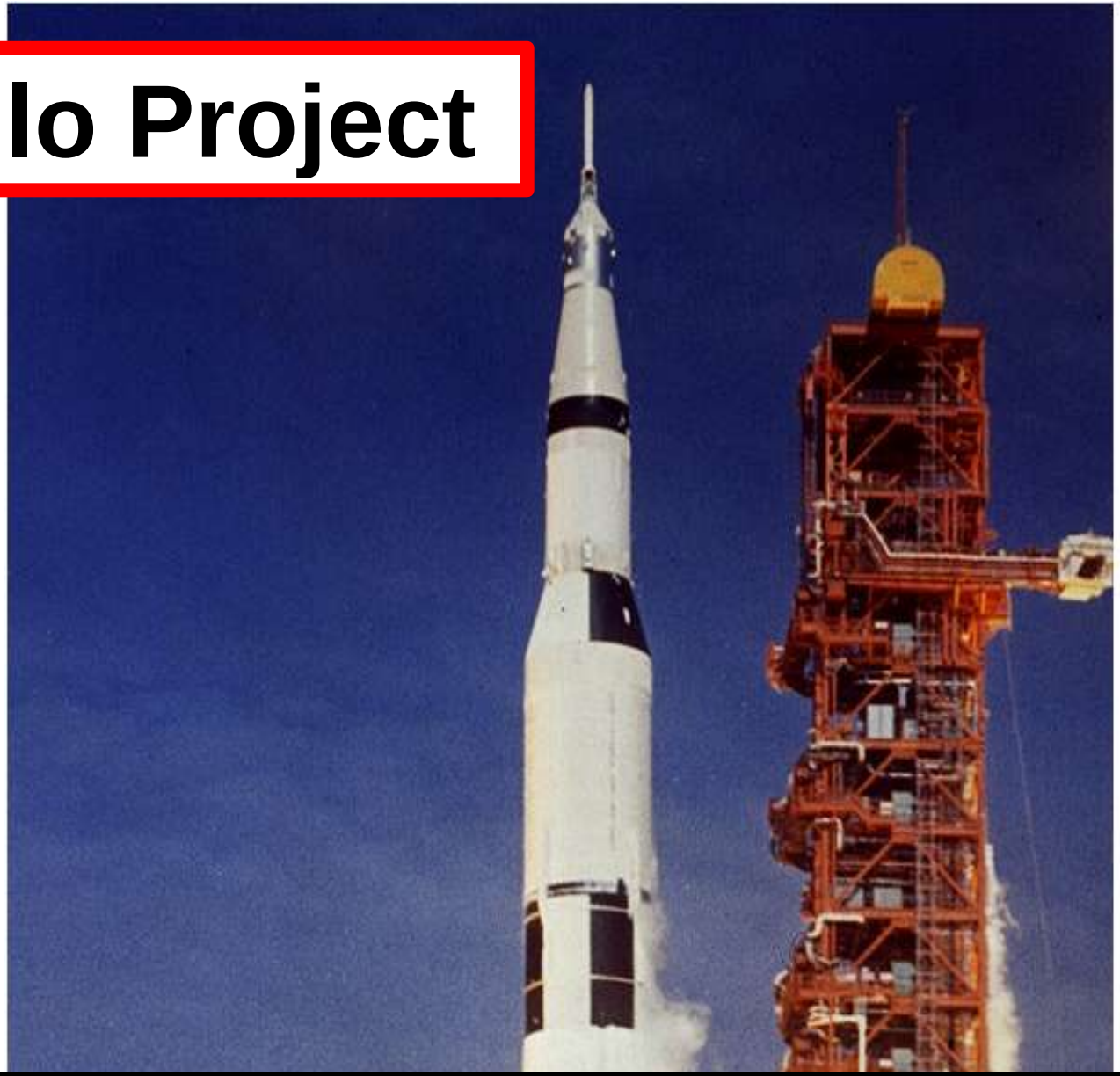
SATURN



Apollo Project



Apollo Project



The final cost of project Apollo was reporte to Congress as $25.4 billion in 1973.

Apollo Project

Technology Assessment history starts so early…

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Apollo Project

…nel 1967.. nel decidere se inviare un uomo sulla luna…

- …un **senatore americano** disse:

A policymaker cannot judge the merits or consequences of a technological program within a strictly technical context. He has to consider **social, economic, and legal implication of any course of action**…"

(U.S. Congress, House of Representatives, Congressman Emilio Daddario, 1967)

Anni ‘70

…chi ricorda i primi pressurometri “SPACELAB”??

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Le caratteristiche dell'HTA

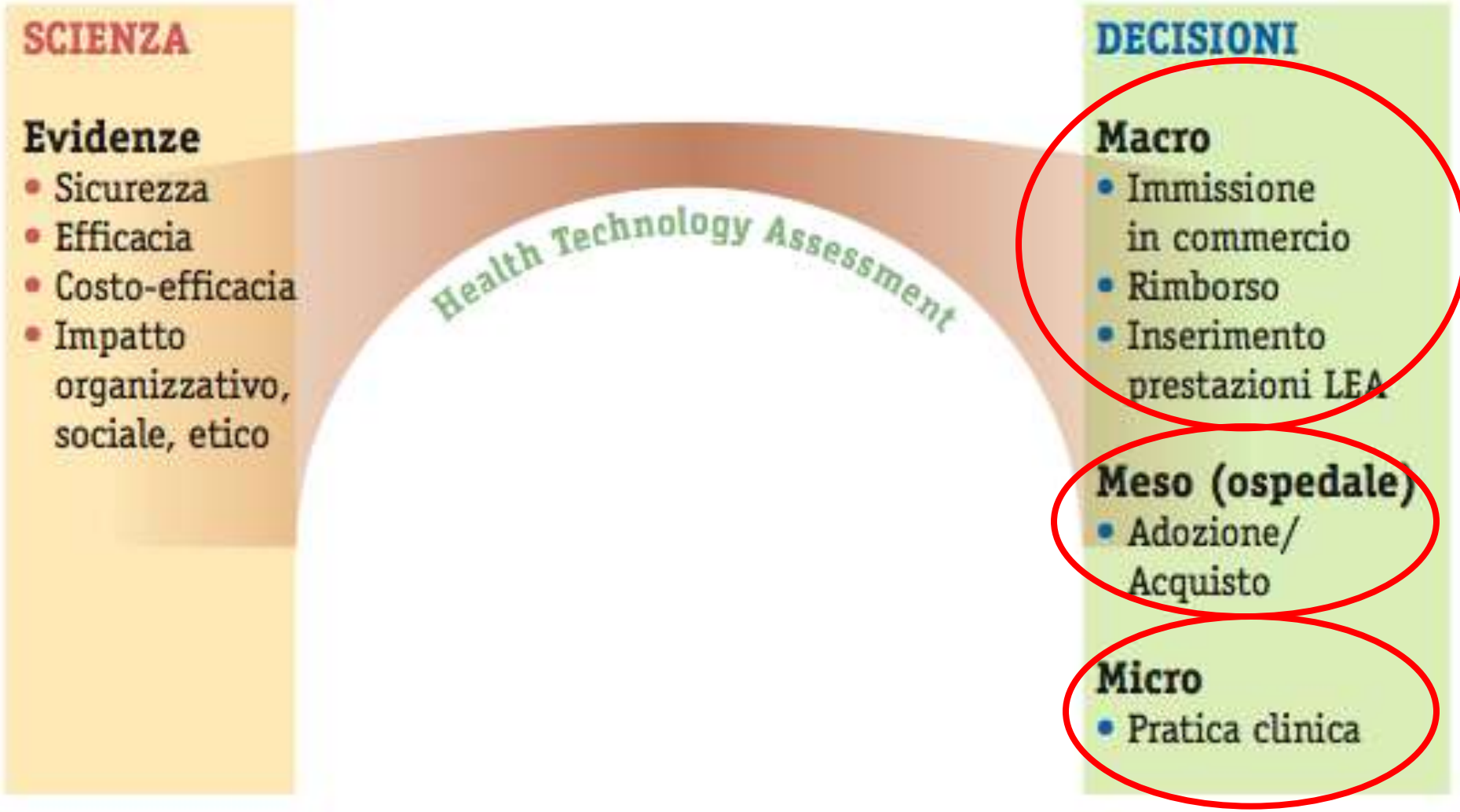
- **Multidisciplinarietà/Multidimensionalità**: perché l'impatto della tecnologia deve essere valutato da diverse prospettive.

- **Strutturalità**: perché presuppone la raccolta e l'analisi sistematica dei dati e delle evidenze a supporto dell'uso delle tecnologie oggetto di valutazione;

- **Orientamento politico**: perché opera da "**ponte**" tra il mondo scientifico e quello politico-decisionale e si configura come processo **policy - driven**.

Banta D, Behney CJ, Andrulis DP, 1978.

L'Health technology assessment: il ponte tra scienza e decisione



RN Battista, 199

Ambiti di applicazione dell'HTA

- **Farmaci**
- **Biologici** *(vaccini, ….)*
- **Dispositivi medici** *(invasivi (impiantabili e non), non invasivi, di diagnostica in vitro…)*
- **Grandi apparecchiature** *(diagnostiche: bioimmagini, valutazione funzionale; terapeutico- riabilitative: organi artificiali/protesi, riabilitazione/supporto…)*
- **Procedure mediche e chirurgiche**
- **Procedure organizzative e sistemi di gestione**
- **Sistemi informativi**

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società italiana di health technology assessment

Cosa si fa nell'HTA

L'HTA si focalizza, quindi, sui seguenti aspetti correlati alla tecnologia:

Performance tecnica
Efficacia
Sicurezza

→ **TECNOLOGIA**

→ **PAZIENTE**

Effetti clinici, implicazioni etiche, legali e sociali

Costi e costo-efficacia → **ECONOMIA**

Ripercussioni organizzative → **ORGANIZZAZIONE**

Health Technology Assessment (HTA)

- HTA systematically evaluates properties, effects, and/or impacts of existing or new healthcare technologies.

- The results of HTA are mostly implemented through clinical practice guidelines. One important method used for HTA is EBM.

Forward Look – Implementation of Medical Research in Clinical Practice – EU 2001

Determinanti della adozione e della diffusione delle innovazioni

- Le loro caratteristiche intrinseche

1. Relative advantage
2. Compatibility
3. Low complexity
4. Trialability
5. Observability

Efficacy versus effectiveness

Efficacy : The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result **under ideal conditions**.

Effectiveness : The extent to which a specific intervention, etc., **when deployed in the field**, does what is intended to do for a defined population. (J. M. Last, A Dictionary of Epidemiology.)

- Valutazione economica → studi pragmatici
- Evidence based medicine
- Valutazione economica basata sull'evidence based medicine

↓

Efficiency based medicine

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Tecniche di valutazione economica

Analisi	Costi	Risultati	Utilizzo	Vantaggi	Svantaggi
Costo-Beneficio	Misurati in moneta	Misurati in moneta	Basso	Si possono confrontare tecnologie con differenti indicatori di efficacia e anche tecnologie al di fuori della sanità. Si tiene conto del valore economico espresso dal paziente per i risultati della tecnologia	La stima monetaria dei benefici si affida a tecniche in parte ancora controverse L'efficacia è di difficile comprensione. E' lontana dalle discipline non economiche.
Costo-Efficacia	Misurati in moneta	Misurati in unità naturali (anni di vita, guarigioni, ecc.)	Molto alto	L'efficacia è di immediata comprensione e non richiede traduzioni in altri indicatori complessi. E' più vicina alle discipline non economiche.	Permette confronti solamente fra tecnologie analoghe (es. diagnostiche per la stessa patologia), tranne quando l'efficacia è espressa in anni di vita. Richiede sempre l'analisi incrementale.
Costo-Utilità	Misurati in moneta	Misurati in QALYs (anni di vita ponderati per la qualità)	Medio	Tiene conto dell'impatto sulla qualità di vita. Permette il confronto fra tecnologie di ambiti terapeutici e diagnostici differenti	La stima dell'efficacia (QALY) richiede strumenti ancora controversi e di difficile applicazione Richiede sempre l'analisi incrementale.

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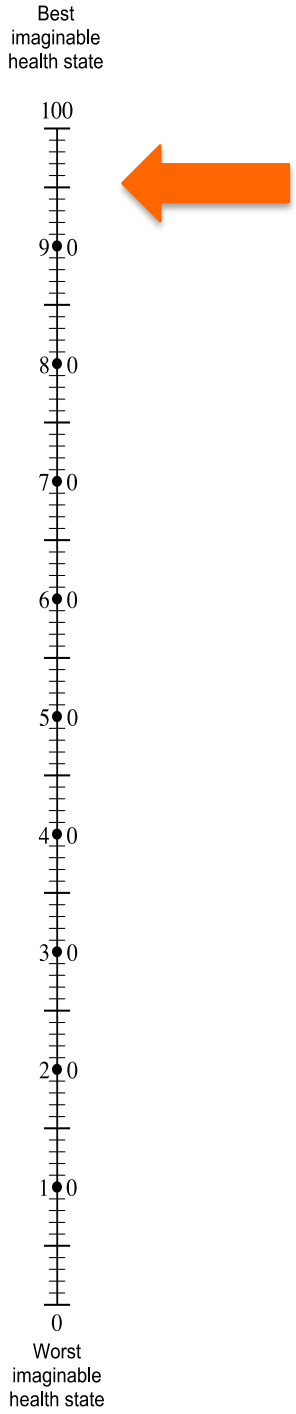
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Valutazione economica:
un solo principio fondamentale

A = trattamento innovativo

B = trattamento standard

Confronto clinico A vs B:

se A non è significativamente più efficace di B:

Paghiamo A non più di quanto stiamo già pagando B

se A è significativamente più efficace di B:

Paghiamo A più di B (accettando un incremento di spesa purchè proporzionato all'aumento di beneficio*)

*Quindi: il costo per QALY guadagnato per A vs B è stato calcolato ed è accettabile.

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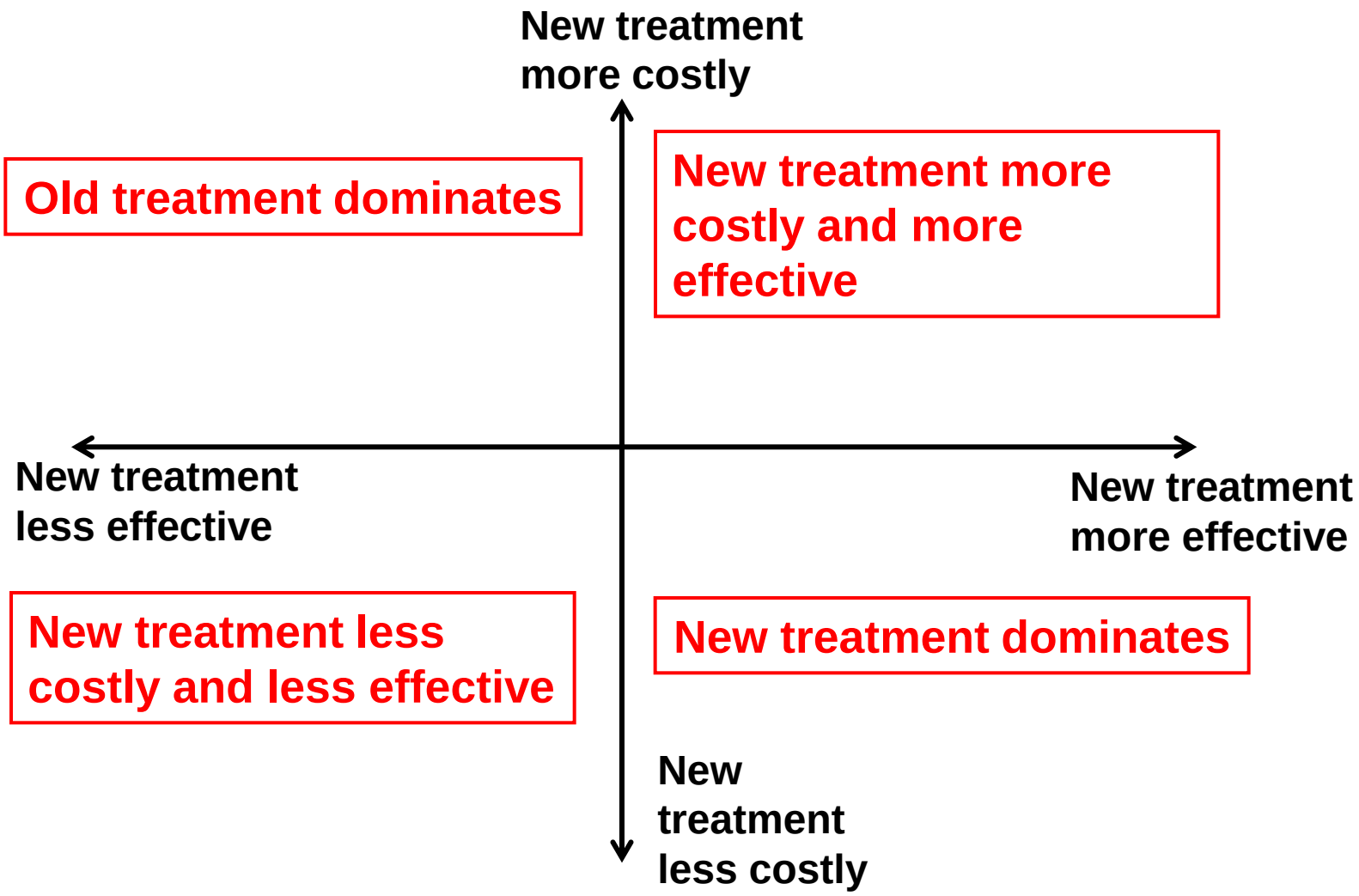
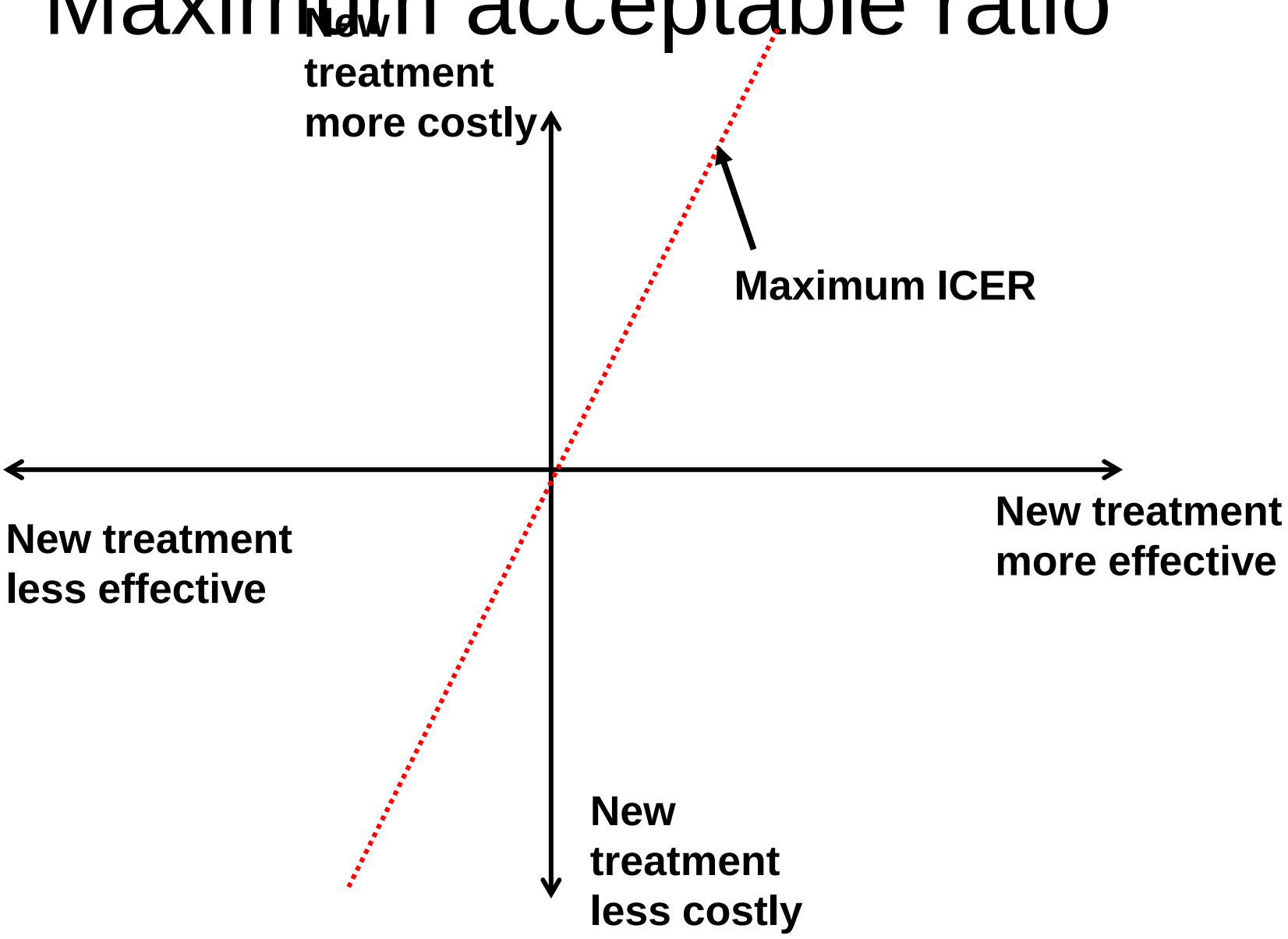
Incremental cost-effectiveness plane



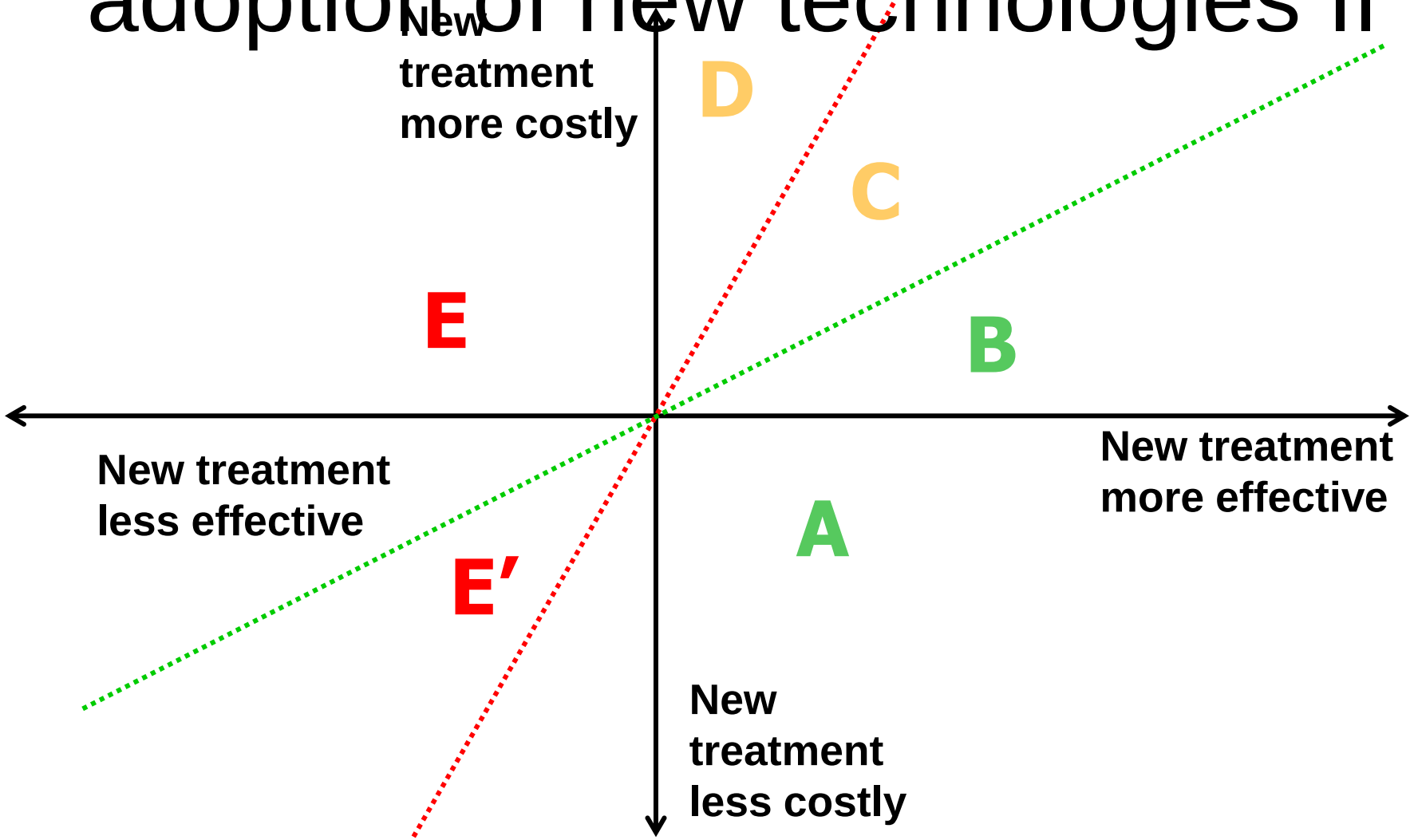
Maximum acceptable ratio



Grades of recommendation for adoption of new technologies

- **A**: **Compelling evidence for adoption**
  - New technology is as effective, or more effective, and less costly
- **B: Strong evidence for adoption**
  - New technology more effective, ICER ≤ $20,000/QALY
- **C: Moderate evidence for adoption**
  - New technology more effective, ICER ≤ $100,000/QALY
- **D: Weak evidence for adoption**
  - New technology more effective, ICER > $100,000/QALY
- **E: Compelling evidence for rejection**
  - New technology is less effective, or as effective, and more costly

Grades of recommendation for adoption of new technologies II



Indicatori nell'approccio "value for money"

- Costo per QALY guadagnato:
  -valore basso (favorevole) = "soldi spesi bene"
  -valore alto (sfavorevole) = "soldi spesi male"

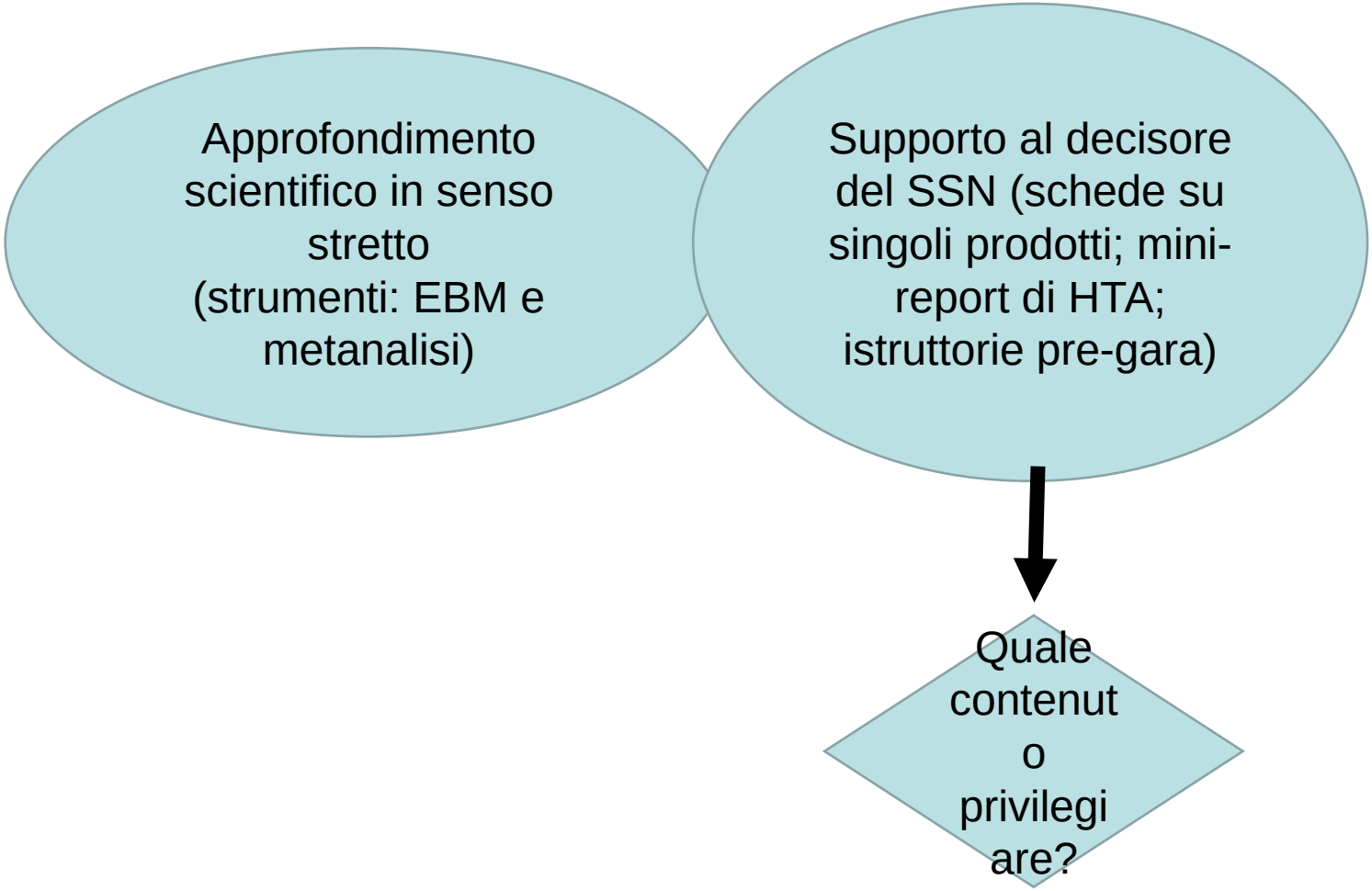
- Valore soglia del costo per QALY guadagnato:
  -circa
- **50mila euro o**
- **60mila dollari o**
- **25mila sterline**;
  da cui: ogni mese viene valorizzato attorno a 5mila euro

Classifica dei costi per QALY

Trattamento	Costo/QALY (Sterline 1990)
Dialisi ospedaliera per disfunzioni renali	22.000
By-pass coronarico, angina moderata	19.000
Dialisi ambulatoriale per disfunzioni renali	18.500
Ceftazidime per fibrosi cistica	11.500
Screening per il tumore alla mammella	5.000
Gomma alla nicotina per fumatori maschi, età 65-69	5.000
Trapianto di rene	4.500
Gomma alla nicotina per fumatori maschi, età 35-39	3.750
Scoliosi idiopatica dell'adolescente	3.500
Sostituzione dell'articolazione alla spalla	1.000
By-pass coronarico, angina grave	1.000
Scoliosi + malattia neuromuscolare	200

Adattato da Parsonage e Neuburger (1992).

L’attività di HTA: come miscelare i vari ingredienti



Valuing the clinical benefit: setting priority on simplicity..

- Main criterion:

Each month of life gained is valued €5,000*

*The corresponding yearly threshold is € 60,000 per life year gained.

AIFA Editorial 13/03/2014

Il value-based pricing è la soluzione

A quale dei due criteri va data dunque priorità? Va tentato un compromesso? La questione resta di difficilissima soluzione. Come abbiamo osservato [1], una risposta, anche se orientata fin troppo speculativamente verso una teorica ricerca del "giusto", può forse venire dall'esame del seguente scenario ipotetico. Immaginiamo che il produttore di Avastin decida di richiedere l'indicazione intravitreale e si presenti in CPR per negoziare una presunta nuova specialità a somministrazione intravitreale.

Andrea Messori e Mauro De Rosa

13 Marzo 2014

“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

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 26, 2015

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

… Although the precision medicine initiative will probably yield its greatest benefits years down the road, there should be some notable near-term successes. In addition to the results of the cancer studies described above, studies of a large research cohort exposed to many kinds of therapies may provide early insights into pharmacogenomics — **enabling the provision of the right drug at the right dose to the right patient.**

Opportunities to identify persons with rare loss of function mutations that protect against common diseases may point to attractive drug targets for broad patient populations. And observations of beneficial use of mobile health technologies may improve strategies for preventing and managing chronic diseases. …

- **Each time you administer a medication, you need to be sure to have the:**
- **1. Right individual**
- **2. Right medication**
- **3. Right dose**
- **4. Right time**
- **5. Right route**
- **6. Right documentation**

- **BDS Medication Administration Curriculum Section IV 2011**

The Precision Medicine Initiative: Data-Driven Treatments as Unique as Your Own Body

Lindsay Holst

January 30, 2015
09:19 AM EST


THE PRECISION MEDICINE INITIATIVE


THE PRECISION MEDICINE INITIATIVE

by **clinical expertise** we mean the ability to use our clinical skills and past experience to rapidly identify **each patient's unique health state and diagnosis**, their **individual** risks and benefits of potential interventions, and their personal values and expectations.

BMJ

BMJ 2014;348:g3725 doi: 10.1136/bmj.g3725 (Published 13 June 2014)

ANALYSIS

Evidence Based Medicine Renaissance

ESSAY

Evidence based medicine: a movement in crisis?

Trisha Greenhalgh and colleagues argue that, although evidence based medicine has had many benefits, it has also had some negative unintended consequences. They offer a preliminary agenda for the movement's renaissance, refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment

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