Disegno dello studio e tassonomia degli studio

Center Bicocca Bioinformatics, Biostatistics and Bioimaging (B4) – School of Medicine and Surgery

University of Milano-Bicocca

- Obiettivo:

Apprendere i principi fondamentali della ricerca biomedica, in particolare i tipi di studio utilizzati per produrre dati su questioni di tipo clinico, siano esse sul trattamento, sulla prevenzione o sulla descrizione di malattie ecc…

Ricerca biomedica: definizione

Insieme di studi con finalità mediche tesi a stabilire una relazione tra una caratteristica o un intervento (trattamento) ed una malattia o una condizione predisponente ad una malattia.

La relazione alla quale si è interessati è quella di **causa-effetto**.

Si tratta di distinguere tra

SEGNALE **RUMORE DI FONDO**

Caratteri distintivi di uno studio clinico o biomedico

- I ragionamenti, i metodi e le conclusioni sono basati sul confronto
- Le conclusioni sono estese dal particolare del campione al generale della popolazione (inferenza) sulla base di un modello statistico-probabilistico
- Tutto è pianificato in dettaglio ed in modo documentato prima dell'inizio dello studio
- Le conclusioni sono basate sul confronto tra gruppi "omogenei"

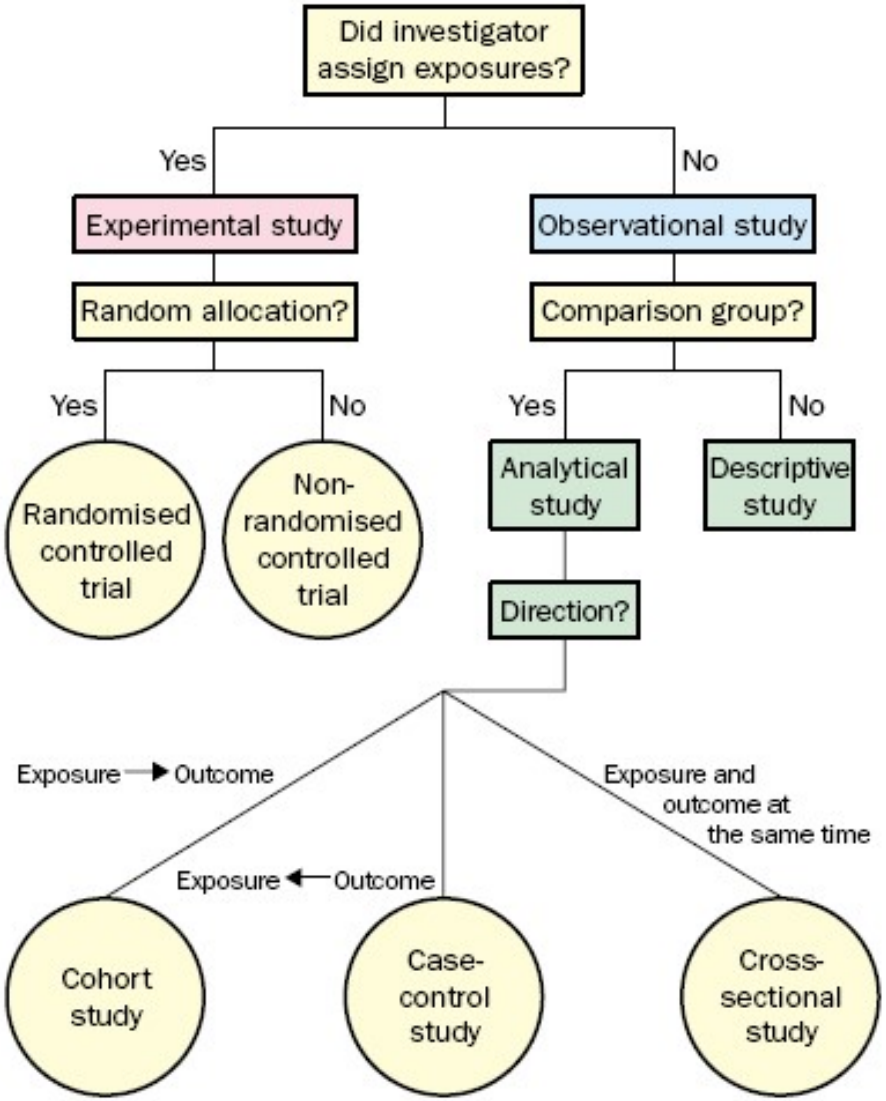
Una tassonomia degli studi nella ricerca clinica

- Clinical research has two large “kingdoms”

Experimental vs observational studies

D.A. Grimes, K.F. Schulz, An overview of clinical research: the lay of the land. Lancet 2002; 359: 57-61

Clinical research has two large "kingdoms"



Studi sperimentali o osservazionali

L'esposizione è assegnata dal ricercatore?

Sì → **Studio Sperimentale**

Implica la modifica (rispetto alla normale pratica clinica) del trattamento per studiarne l'effetto sull'esito. E' condotto in condizioni controllate. Può includere la randomizzazione.

No → **Studio Osservazionale**

La decisione di prescrivere il farmaco al singolo paziente deve essere del tutto indipendente da quella di includere il paziente stesso nello studio (Prescrizione farmaco, procedure diagnostiche e valutative secondo normale pratica clinica) (**AIFA**)

SE PARLIAMO DI FARMACI/TRATTAMENTI

Studi sperimentali o osservazionali

L'esposizione è assegnata dal ricercatore?

Sì → **Studio Sperimentale**

Implica la manipolazione della esposizione (espressa da una o più variabili indipendenti) per studiare l'effetto sull' esito (espresso da una o più variabili dipendenti).

Il ricercatore "manipola" la esposizione

No → **Studio Osservazionale**

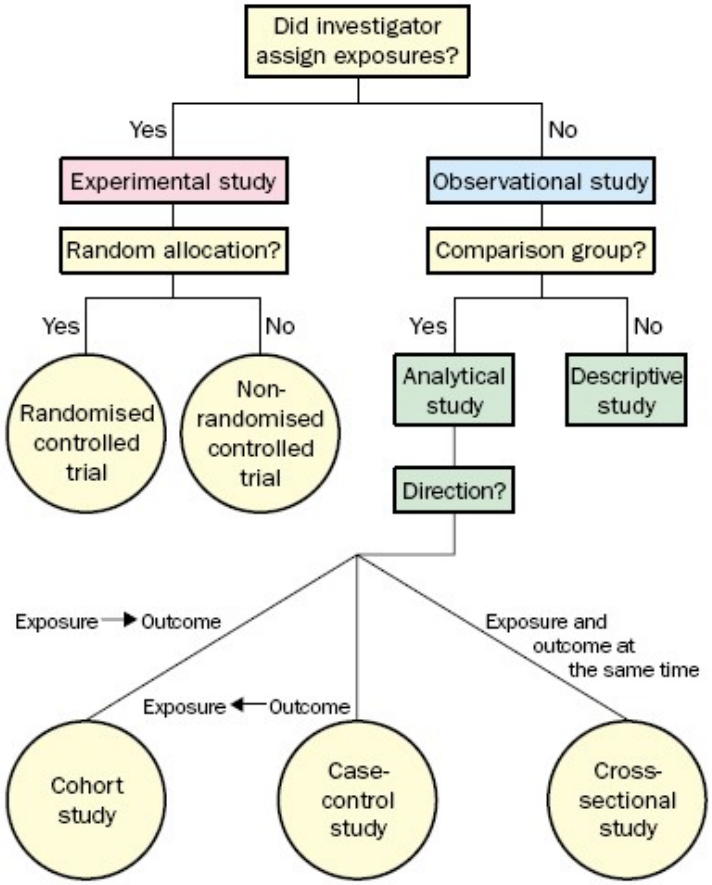
Si studia la relazione tra le differenze in una o più variabili in relazione a differenze in altre variabili senza che il ricercatore intervenga a modificare la esposizione.

Il ricercatore si limita ad osservare.

SE PARLIAMO più in generale di ESPOSIZIONE

Studi Osservazionali

- Percorriamo ora la parte a destra del flowchart



Studi descrittivi

- Danno le informazioni iniziali in nuove aree:
  - frequenza di determinate caratteristiche/fattori;
  - Distribuzione geografica, temporale e demografica;
  - storia "naturale";
  - possibili determinanti di una condizione;
  - sorveglianza sanitaria
- I risultati:
  - Descrivono la distribuzione e le caratteristiche di una patologia e/o dei soggetti affetti;
  - Generano ipotesi di studio sull'eziologia (raramente sul trattamento)

Nella ricerca clinica spesso sono la descrizione di serie di casi

Una definizione necessaria: Casi incidenti e prevalenti

INCIDENT CASES: **new cases presenting the event of interest in a given period of time**

PREVALENT CASES: **all cases who have a given characteristic (i.e.the event of interest) at the moment they are observed**

Esempi studi descrittivi

nella contemporaneità
dell'emergenza COVID 19

danno le informazioni iniziali in
nuove aree

Casi Prevalenti ed Incidenti in Italia di COVID-19, 7 marzo 2020

Fonte: Protezione civile - Sole 24ore

Casi attualmente positivi	Morti	Dimessi/ guariti	Casi TOTALI
5061	233	589	5883
+1145	+36	+66	+1247

+ rappresenta l'incremento rispetto al 6 marzo

Casi Prevalenti ed Incidenti in Italia di COVID-19, 1 marzo 2021

Fonte: Protezione civile - Sole 24ore

Casi attualmente positivi	Morti	Dimessi/ guariti	Casi TOTALI
424.333	97.945	2.416.093	2.938.371
+1966	+264	+10.894	+13.114

+ rappresenta l'incremento rispetto al 28 febbraio

Casi Prevalenti ed Incidenti in Italia di COVID-19, 6 marzo 2022
Fonte: Protezione civile - Sole 24ore

Casi attualmente positivi	Morti	Dimessi/ guariti	Casi TOTALI
1.016.341	155.887	11.853.884	13.026.112
-2.490	+105	+38.274	+35.057

+ rappresenta l'incremento rispetto al 5 marzo

Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China

ZunyouWu, Jennifer M.McGoogan, JAMA, February 24, 2020

Report of the Chinese Center for Disease Control and Prevention Report

- 72 314 Cases (as of February 11, 2020)
- Confirmed cases: 44 672 (62%)
- Suspected cases: 16 186 (22%)
- Diagnosed cases: 10 567 (15%)
- Asymptomatic cases: 889 (1%)

Age distribution (N = 44 672)

- >=80 years: 3%(1408 cases)
- 30-79 years: 87%(38 680 cases)
- 20-29 years: 8%(3619 cases)
- 10-19 years: 1% (549 cases)
- <10 years: 1% (416 cases)

Spectrum of disease (N = 44 415)

- Mild: 81% (36 160 cases)
- Severe: 14%(6168 cases)
- Critical: 5%(2087 cases)

Case-fatality rate

- 2.3%(1023 of 44 672 confirmed cases)
- 14.8%in patients aged >=80 years (208 of 1408)
- 8.0% in patients aged 70-79 years (312 of 3918)
- 49.0% in critical cases (1023 of 2087)

Health care personnel infected

- 3.8%(1716 of 44 672)
- 63% in Wuhan (1080 of 1716)
- 14.8%cases classified as severe or critical (247 of 1668)
- 5 deaths

Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series

BMJ 19 Feb 2020

- OBJECTIVE To study the clinical characteristics of patients in Zhejiang province, China, infected with the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) responsible for coronavirus disease 2019 (covid-2019).
- DESIGN Retrospective case series.
- SETTING Seven hospitals in Zhejiang province, China.
- PARTICIPANTS 62 patients admitted to hospital with laboratory confirmed SARS-Cov-2 infection. Data were collected from 10 January 2020 to 26 January 2020.

Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series

BMJ 19 Feb 2020

- MAIN OUTCOME MEASURES Clinical data, collected using a standardised case report form, such as temperature, history of exposure, incubation period. If information was not clear, the working group in Hangzhou contacted the doctor responsible for treating the patient for clarification. RESULTS Of the 62 patients studied (median age 41 years), only one was admitted to an intensive care unit, and no patients died during the study. According to research, none of the infected patients in Zhejiang province were ever exposed to the Huanan seafood market, the original source of the virus; all studied cases were infected by human to human transmission. The most common symptoms at onset of illness were fever in 48 (77%) patients, cough in 50 (81%), expectoration in 35 (56%), headache in 21 (34%), myalgia or fatigue in 32 (52%), diarrhoea in 3 (8%), and haemoptysis in 2 (3%). Only two patients (3%) developed shortness of breath on admission. The median time from exposure to onset of illness was 4 days (interquartile range 3-5 days), and from onset of symptoms to first hospital admission was 2 (1-4) days.
- CONCLUSION As of early February 2020, compared with patients initially infected with SARS-Cov-2 in Wuhan, the symptoms of patients in Zhejiang province are relatively mild.

Mortalità da COVID-19

Nelle rilevazioni dell'Iss il rapporto tra N.decessi e N.positivi (media su 7 giorni) ovvero il tasso di letalità (Infection Fatality Rate – IFR) è:

-alla data 01/01/21 IFR= 2,73%
-alla data 01/01/22 IFR= 0,21%

Mortality and seroprevalence in 45 countries – Nature, November 2020

COVID Infection-Fatality Rates by Sex and Age Group
(Numbers are shown as percentages)

Age group	Male	Female	Mean
0-4	0.003	0.003	0.003
5-9	0.001	0.001	0.001
10-14	0.001	0.001	0.001
15-19	0.003	0.002	0.003
20-24	0.008	0.005	0.006
25-29	0.017	0.009	0.013
30-34	0.033	0.015	0.024
35-39	0.056	0.025	0.040
40-44	0.106	0.044	0.075
45-49	0.168	0.073	0.121
50-54	0.291	0.123	0.207
55-59	0.448	0.197	0.323
60-64	0.595	0.318	0.456
65-69	1.452	0.698	1.075
70-74	2.307	1.042	1.674
75-79	4.260	2.145	3.203
80+	10.825	5.759	8.292

Younger people are less likely to die after COVID-19 infection and IFR increases with age, sharply after 65 years

Beginning with the 20-24 age group, men are about twice as likely to die as women from COVID and this remains up to 80+

Un "Case report" che ha portato a scoprire una associazione perchè genera un' ipotesi di studio sull'eziologia

- A clinician reported benign hepatocellular adenomas, a rare tumour, in women who had taken oral contraceptives.

Schenken JR. Hepatocellular adenoma: relationship to oral contraceptives? JAMA 1976.

- A large case-control study pursued this lead and confirmed a strong association between long-term use of high-dose pills and this rare, but sometimes deadly, tumour.

Rooks JB, Ory HW, Ishak KG, et al. Epidemiology of hepatocellular adenoma: the role of oral contraceptive use. JAMA 1979

Case Series reports may suggest a false association:

Seven women in Pasadena (Ca) created controversy around the world in the late 1980s. The women had developed functional ovarian cysts while taking the new multiphasic oral contraceptive pills. *Am J Obstet Gynecol* 1987

Within 2 years, a publication showed no temporal association between the marketing of multiphasic pills and the number of women admitted to hospital for treatment of benign ovarian cysts (REAL WORLD STUDY). *Obstet Gynecol* 1989

5 years elapsed before cohort and case-control studies confirmed no association between multiphasic pills and ovarian cysts. *Am J Obstet Gynecol* 1992 and *Obstet Gynecol* 1992;

Studi analitici

Studiano la relazione tra esposizione ed esito

- Epidemiologia: relazione tra intensità di esposizione a fattori di rischio / protettivi e frequenza di malattia
- Epidemiologia clinica: impatto di un trattamento/procedura nella pratica clinica, fattori prognostici, effetti a lungo termine (farmacovigilanza)

Si differenziano per il legame dell'osservazione col tempo

Studi analitici

Studio trasversale: guarda l'associazione di una esposizione con un esito misurati in contemporanea: spesso difficile interpretare causa-effetto

Studio caso-controllo: parte dall'esito e va retrospettivamente a misurare l' esposizione per vedere se vi è associazione

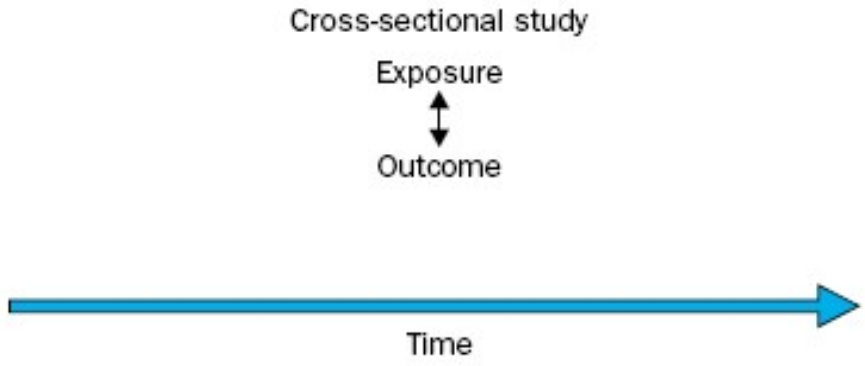
Studio di coorte: parte dalla misura dell'esposizione e valuta prospetticamente l'esito

Cross-sectional study

- Outcome (presence or absence of disease) and exposure are ascertained at the same time.
- Focus is on prevalence

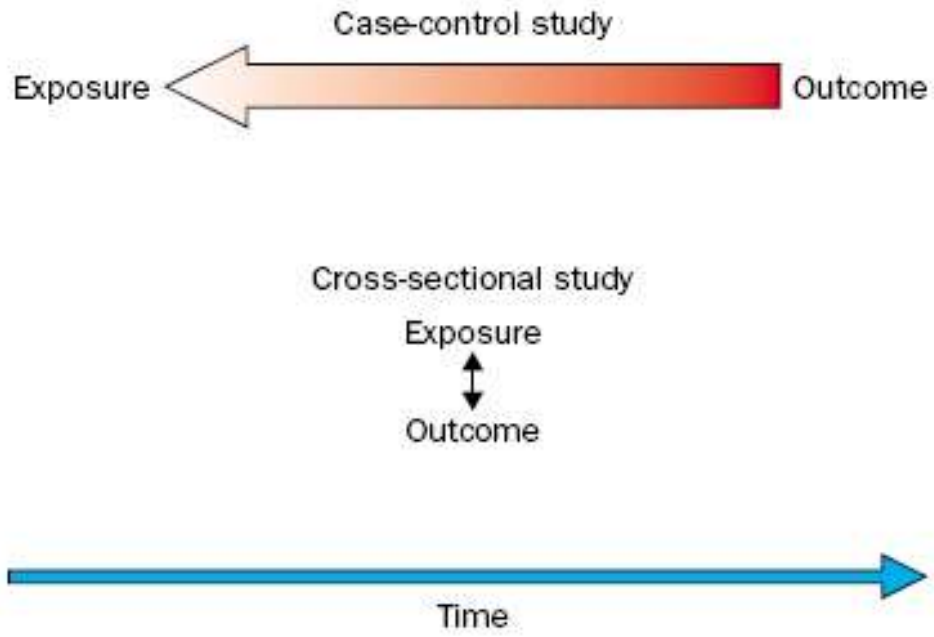
Temporal (causal) relation might be unclear

Ex.: a cross-sectional study finds obesity to be more common among women with than without arthritis. Did the extra weight load on joints lead to arthritis, or did women with arthritis become involuntarily inactive and then obese?



Case-control study

- Starts with outcome and looks backward in time for exposure that might have caused the outcome
- Defines a group with an outcome (*cases*) and a group without (*controls*)
- Ascertains the prevalence of exposure to a risk factor in both groups
- If the prevalence of exposure is higher among cases, then the exposure is associated with an increased risk of the outcome



Case-control study

Outbreaks of food-borne diseases on a cruise ship. Those with vomiting and diarrhoea are asked about food exposure, as are a sample of those not ill. If a higher proportion of those ill reports having eaten a food than those well, the food becomes suspect.

Case-control study

Strenghts:

- useful for rare outcomes or that take a long time to develop
- requires less time, effort, and money than cohort study

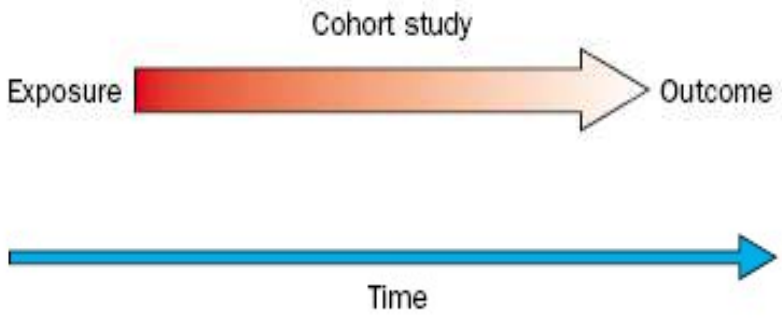
Weaknesses:

- choosing an appropriate control group
- recall bias (bias due to effect of memory)
- cannot calculate incidence rates, relative risk or attributable risk

Association is measured with **ODDS RATIOS**, good proxy for the true relative risk (especially if risk is relatively low)

Cohort study

- Proceeds from exposure to outcome
- Identifies a group with an exposure
- Follows the exposed and unexposed groups to determine outcomes
- If the exposed group develops a higher incidence than the unexposed, then exposure is associated with an increased risk of the outcome



Cohort study

Use of Proton Pump Inhibitors (PPI) is related to an increased risk of dementia in elderly?

A cohort of 73679 people aged ≥ 75 y and free of dementia at baseline was monitored for use of PPI and followed up. The 2950 patients receiving regular PPI medication had a significantly increased risk of incident dementia compared with those in the cohort not receiving PPI (70729 patients in the cohort).

Cohort study

Strenghts:

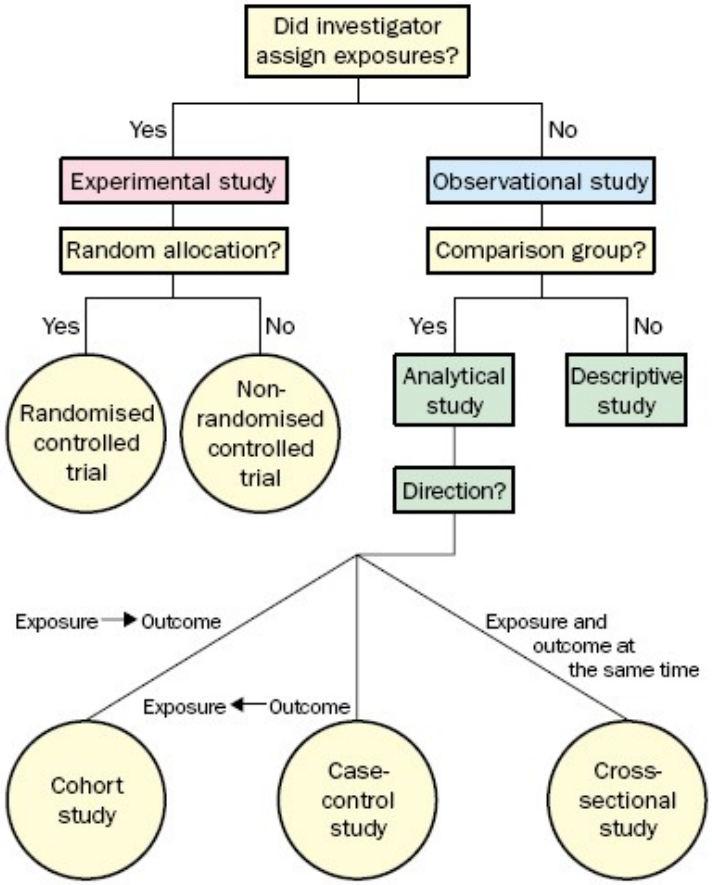
- Recall bias* is less of a concern
- Enables calculation of true incidence rates, relative risks and attributable risks
- Best for causal interpretation

Weaknesses:

- Slow results with rare events or events that take years to develop
- Higher costs

Studi Sperimentali

- Percorriamo ora la parte a sinistra del flowchart



Studi sperimentali che riguardano il trattamento

In mancanza di un gruppo di controllo, non è possibile valutare se vi sia associazione trattamento-esito ovvero:

l'effetto di un trattamento (sperimentale)

è sempre quantificato relativamente ad un trattamento di controllo (standard o placebo)

NB: in generale, in uno studio osservazionale il confronto di outcome di trattamenti diversi non riflette solo l'effetto del trattamento stesso

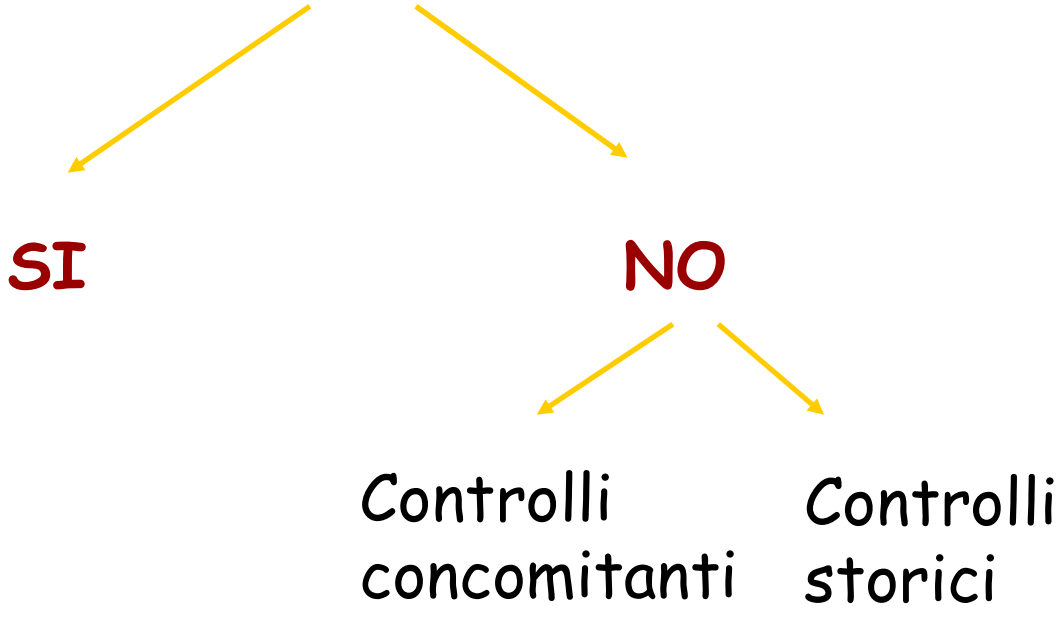
Esposizione=trattamento

Studi sperimentali sul trattamento

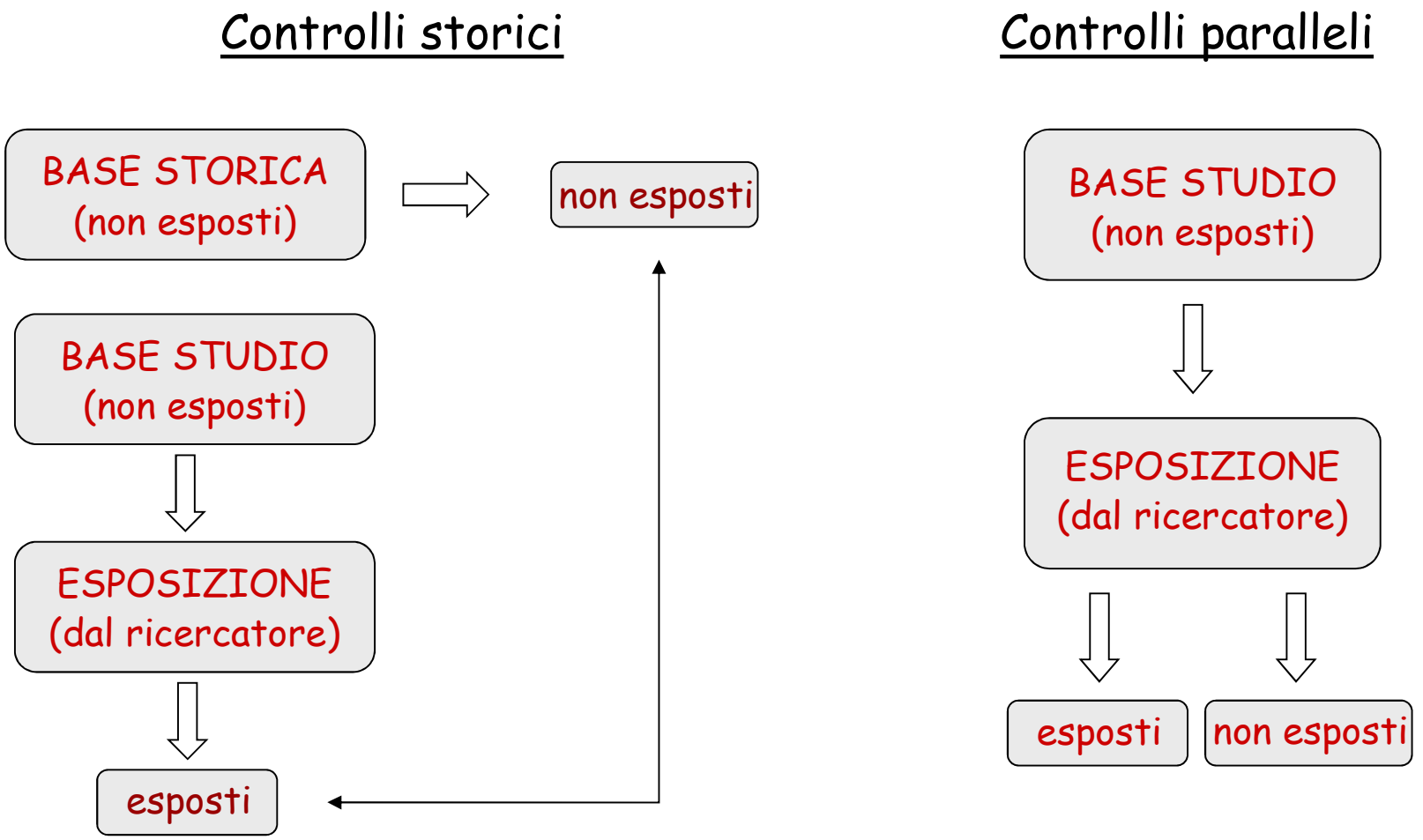
Sono studi prospettici controllati in cui si definisce

gruppo di controllo

randomizzato

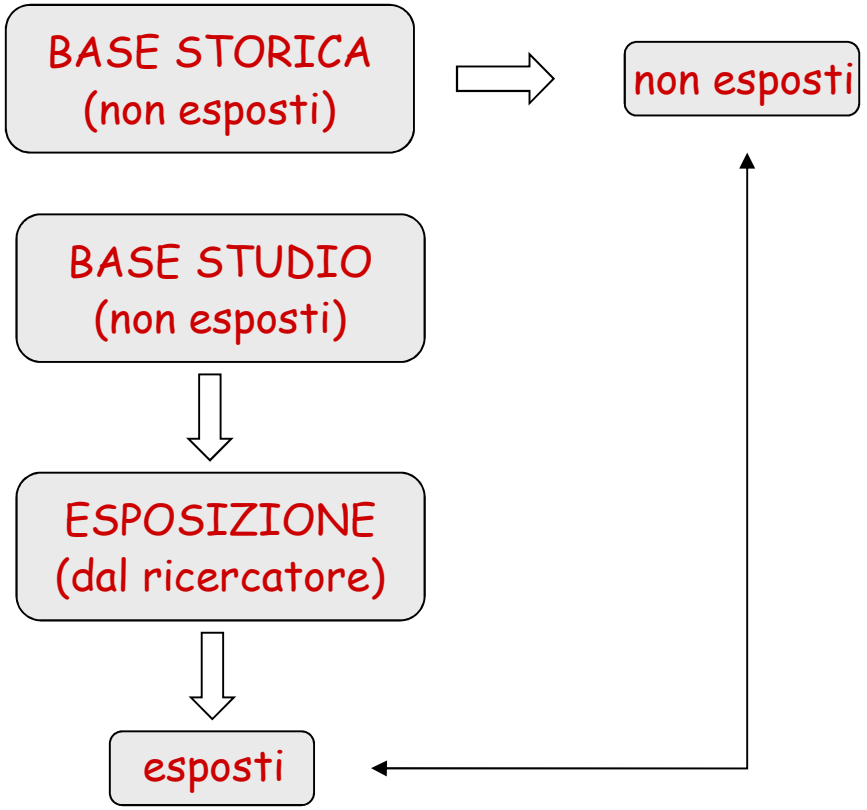


Studi sperimentali non randomizzati



Il contrasto fra i gruppi confrontati stima l'effetto atteso del trattamento nei futuri malati

Studi con controlli storici



- I risultati vengono confrontati con pazienti simili osservati in precedenza nello stesso centro
- Rapido e poco costoso
- Altre fonti di dati storici:
  - Letteratura
  - Banche dati
- Si assume che i soggetti di controllo siano sovrapponibili ai soggetti esposti

E' veramente così?

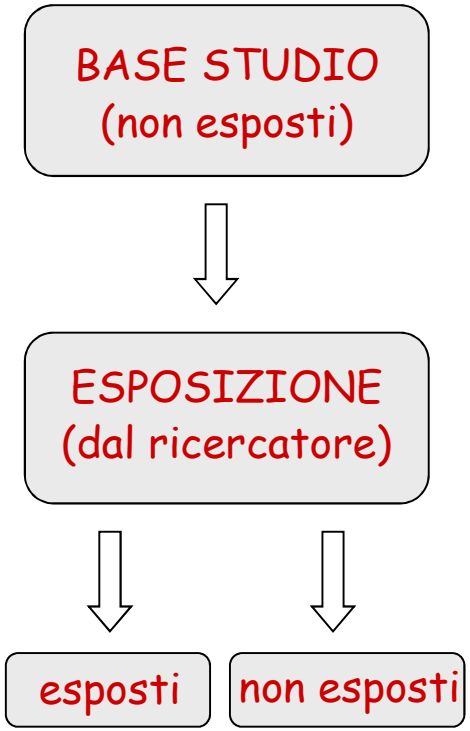
Studi con controlli storici

In realtà gli studi con controlli storici si prestano facilmente ad errori sistematici perché variazioni dell'esito nel tempo si possono avere per…

- variazioni nelle caratteristiche dei soggetti
- variazioni nei criteri di selezione dei soggetti
- variazioni nelle modalità di diagnosi e di assistenza dei pazienti
- variazioni nei criteri diagnostici
- variazioni nella qualità dei dati

Studi non randomizzati con controlli concomitanti

Controlli non randomizzati



- Bias di indicazione
- Preferenze del medico o del paziente
- Differenti modalità di assistenza

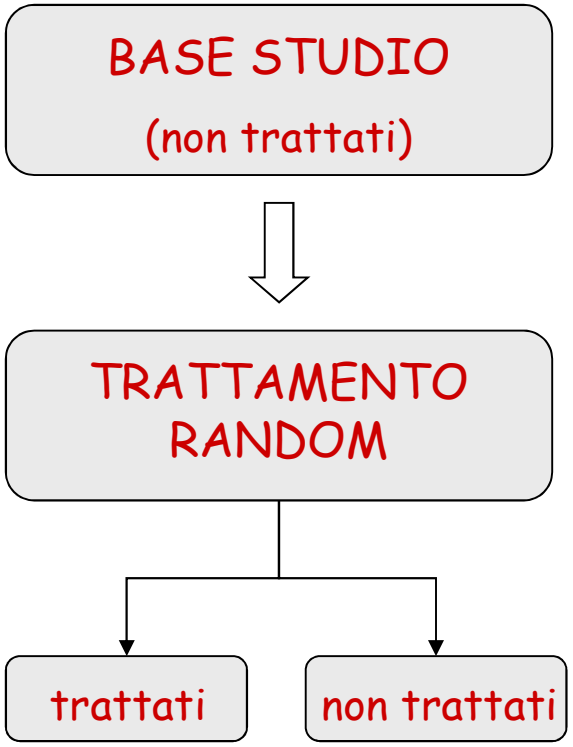
Il contrasto stima l'effetto atteso del trattamento nei futuri malati ?

Studi randomizzati

Tutti i pazienti hanno la stessa probabilità di ricevere uno dei trattamenti studiati.

I controlli sono per disegno concomitanti

Controlli randomizzati (RCT)



La randomizzazione

- Ripartisce casualmente fra i gruppi i fattori prognostici (noti e ignoti)
- Elimina gli errori sistematici nell'assegnazione dei trattamenti ai malati (consapevoli e inconsapevoli)
- E' il modo più eticamente accettabile di assegnare i malati ai trattamenti confrontati
- I risultati sono più credibili
- Garantisce la validità dei test statistici

Avoids selection bias and confounding

Reduces information bias

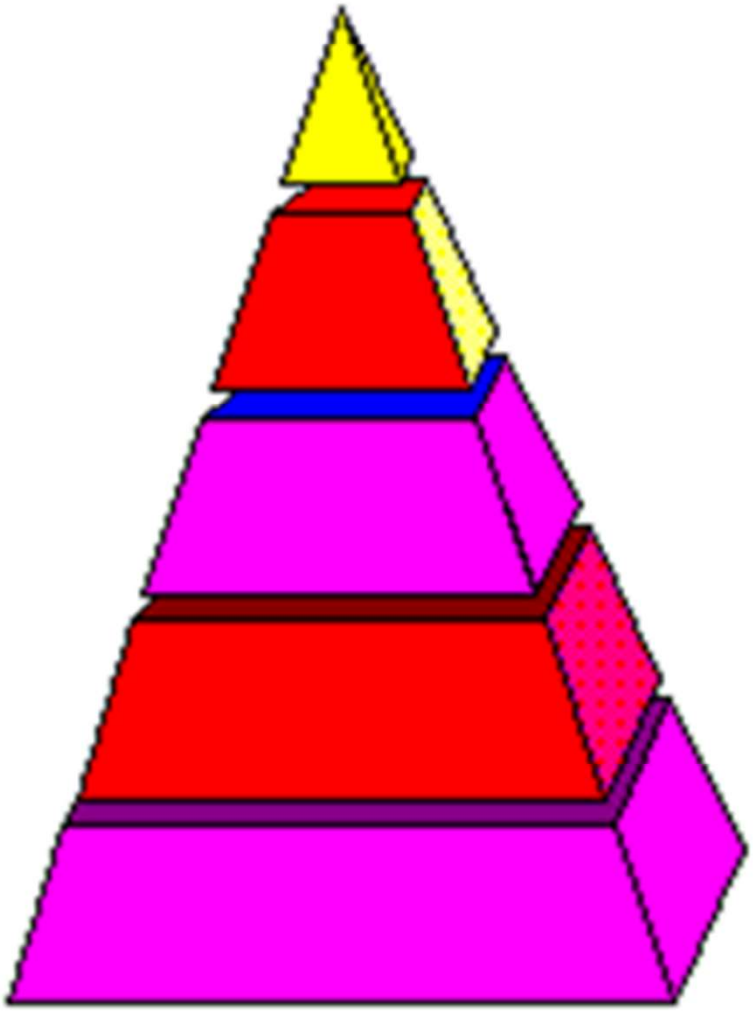
Randomizzazione

- Assegnazione "a caso" e non "a casaccio"!

Le tecniche di randomizzazione sono molteplici e sostanzialmente basate sulla generazione di stringhe di numeri casuali

– non si approfondisce qui l'argomento

Hierarchy of evidence



- Randomized Controlled Trials
- Cohort Studies
- Case Control Studies
- Case Series/ Case Reports
- Opinions, letters
- Animal research
- In vitro research

In generale….

- Molte considerazioni metodologiche sono comuni agli studi sperimentali ed osservazionali….

- Entrambi i tipi di studio necessitano di un protocollo

CARATTERISTICHE DI UN BUON PIANO DI STUDIO

Un buon piano di studio, per portare a conclusioni **affidabili** e **riproducibili**, deve avere le seguenti caratteristiche:

- ✓ **Validità:**
  l'effetto osservato in corrispondenza di un trattamento (o esposizione) deve poter essere attribuito, senza ambiguità, al trattamento stesso
- ✓ **Precisione:**
  in uno studio valido, l'effetto osservato e quello vero differiscono a causa della variabilità casuale. Lo studio è tanto più preciso quanto più si riesce a limitare tale variabilità.
- ✓ **Applicabilità:**
  lo studio deve consentire di generalizzare le conclusioni.

CARATTERISTICHE DI UN BUON PIANO DI STUDIO

Validità: ⇒ Randomizzazione

Precisione: ⇒ Dimensione campionaria

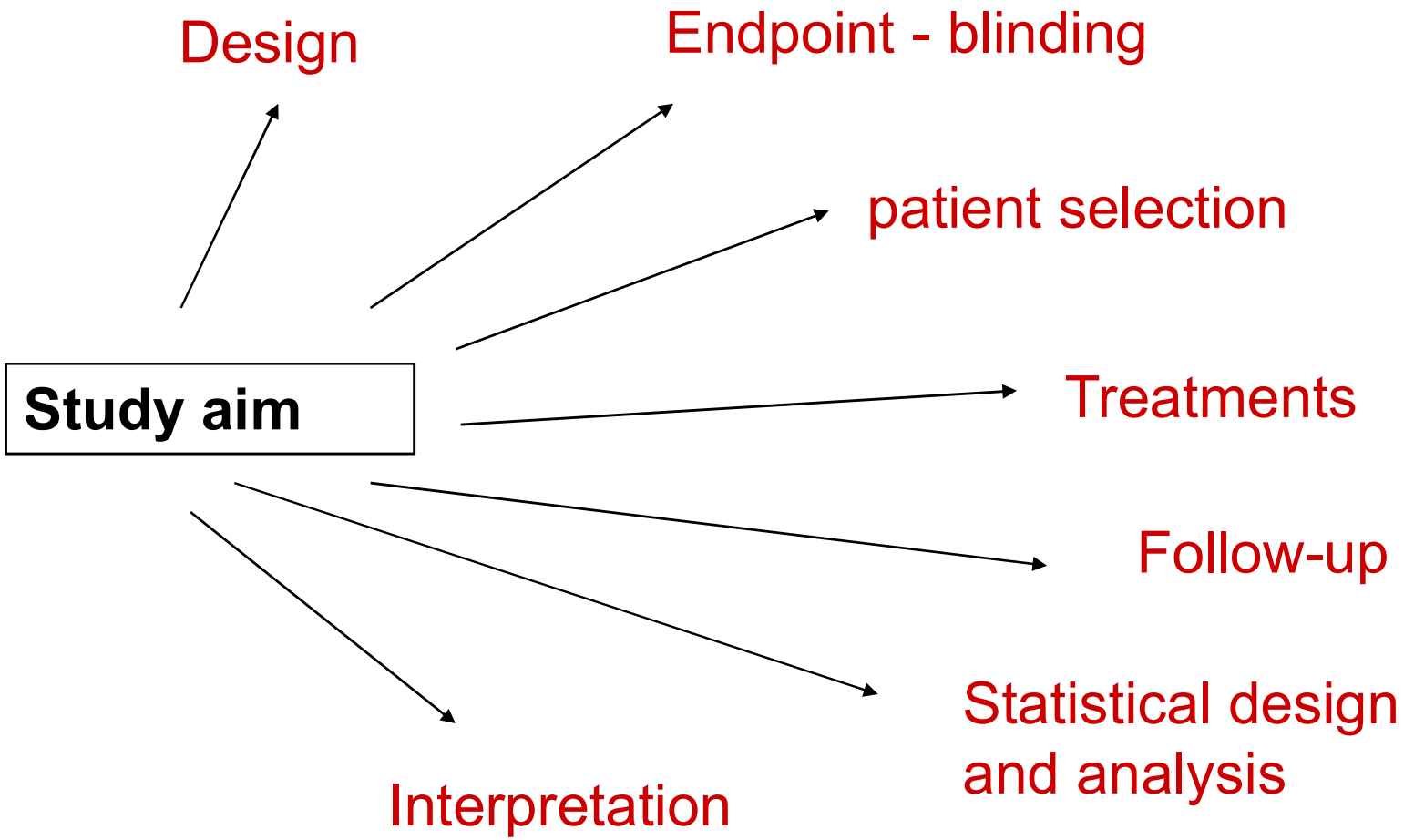
Applicabilità ⇒ Popolazione di riferimento?
procedure?
(criteri eleggibilità, modalità di applicazione del protocollo…)

Medicina di precisione

Approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person in order to allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people - a data-driven approach

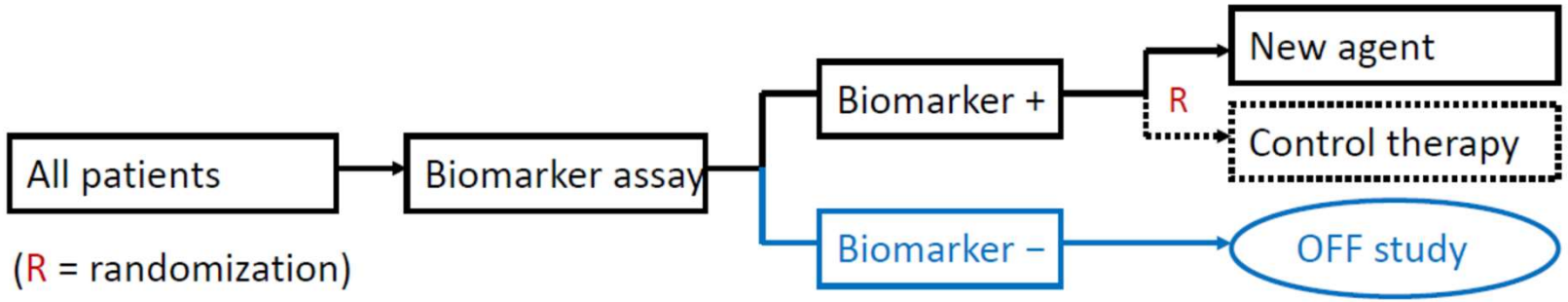
- Valgono comunque i principi visti sui disegni di studio
- Sono stati definiti nuovi disegni di studio basati su biomarcatori ed alcuni esempi sono mostrati qui di seguito

I principi: a good study
Asks a relevant questions
Finds a reliable answer



Biomarker-enrichment design

- Based on knowledge of biology & mechanism
- New agent→Molecular target
- Control therapy arm controls for biomarker prognostic effect
- Variation: Standard therapy ±new agent



Limitations:

- Off-target effects of new agent not fully evaluated
- Regulatory indication limited to biomarker positive group
- Biomarker refinement within trial (biomarker or assay) limited to biomarker positive subgroup

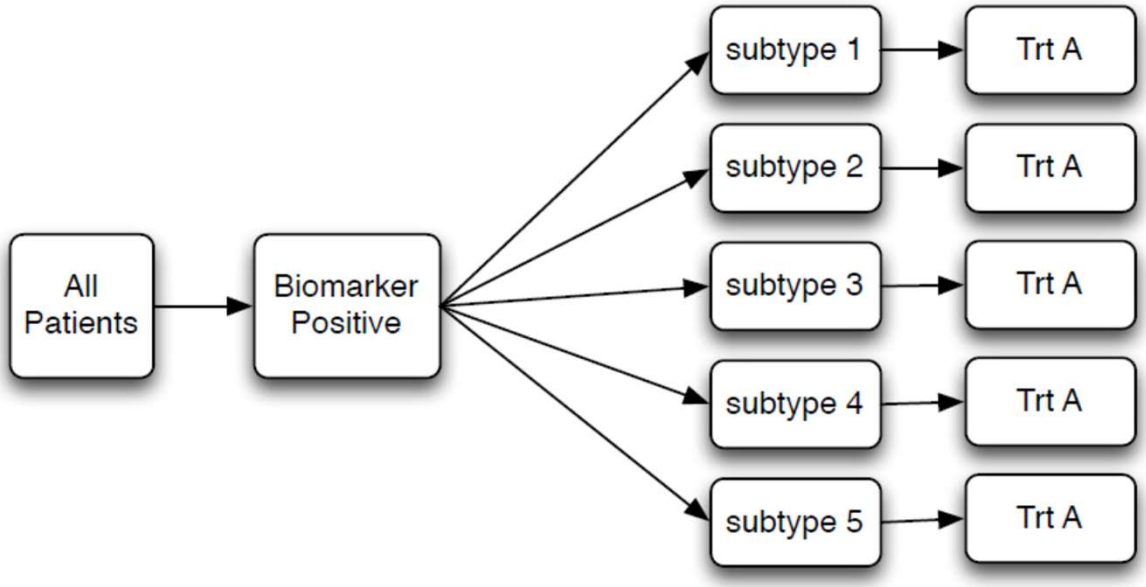
Biomarker Driven Clinical Trials

- Basket Trials: Single treatment and single biomarker, different histologies placed in baskets

- Umbrella Trials: Single histology, multiple biomarkers each matched to treatments

Basket Trials

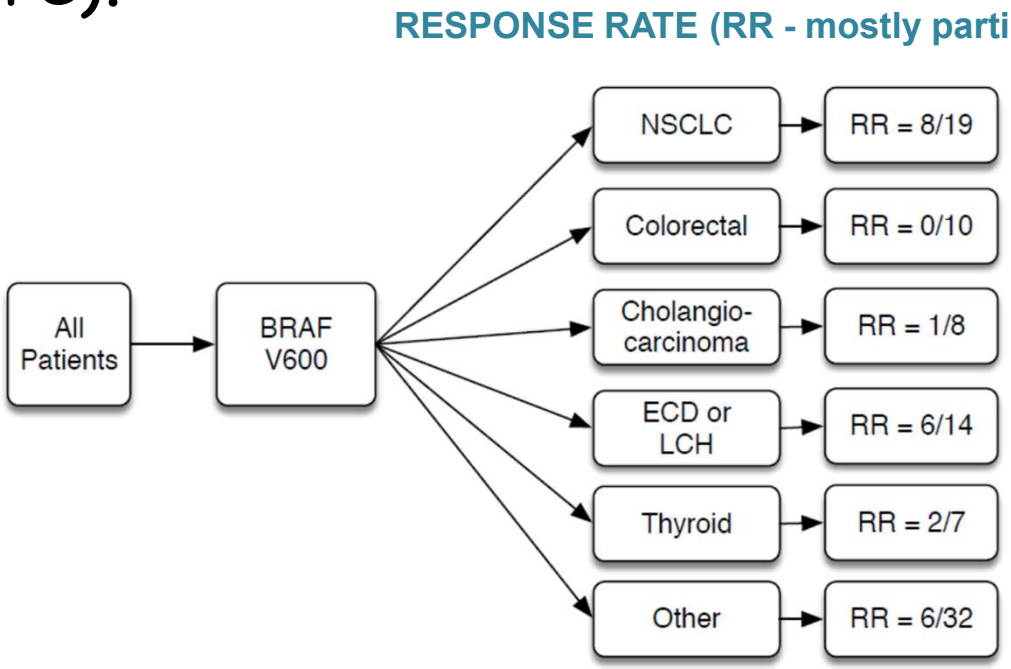
Evaluate the effect of a specific treatment within a biomarker positive subgroup in a variety of tumor types



Basket Trials- an example

Non melanoma cancers with BRAF V600 Vemurafenib mutations treated with Vemurafenib

- 122 patients with BRAF V600 mutations from 5 pre-specified cancers plus an "other" basket (mixture).



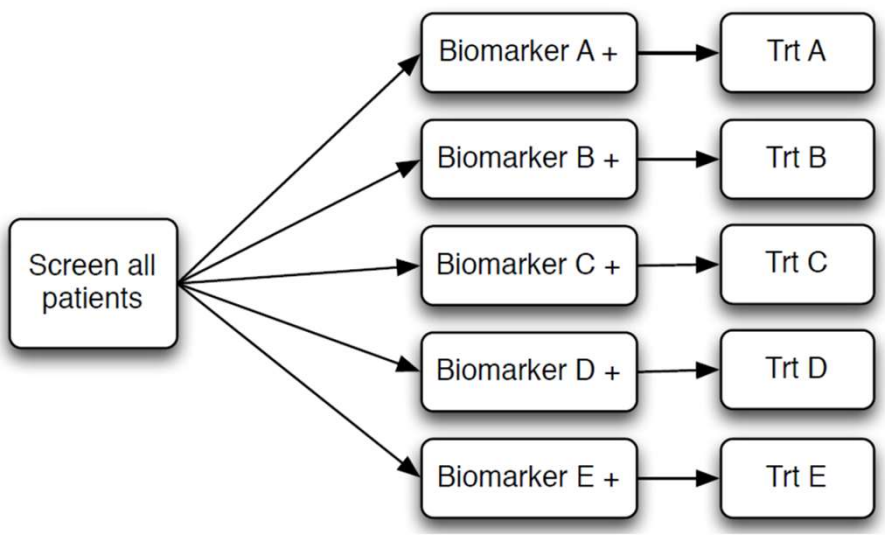
Hyman *et al.* Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*, 2015

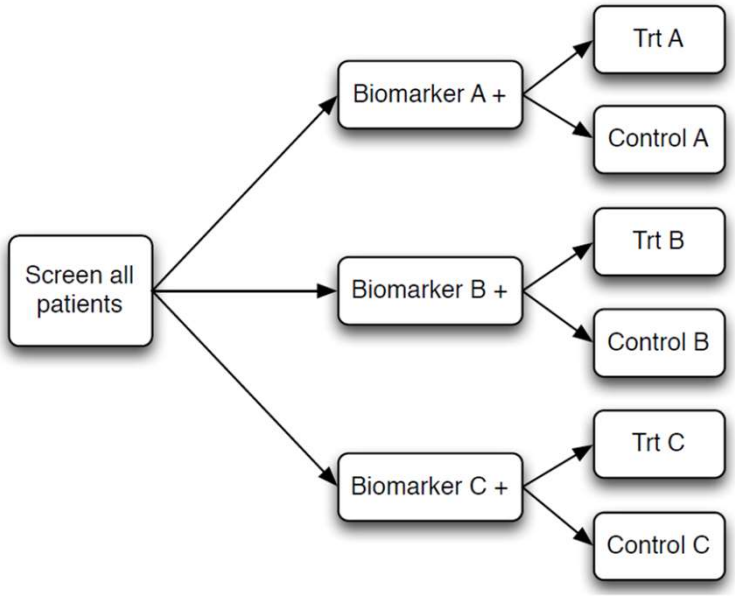
Umbrella Trials

Evaluate many treatments within a single histology.

A multiplex assay is used for treatment arm eligibility.

Each arm is a biomarker enrichment design (one arm or randomised).





Examples: Lung-MAP (SWOG) and FOCUS4 (UK)

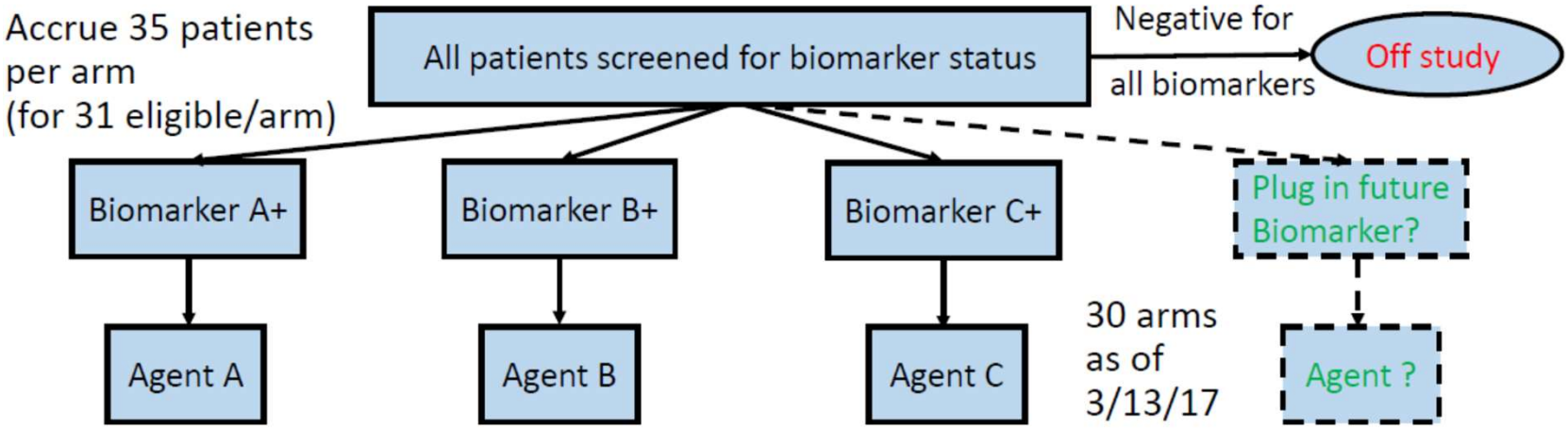
The MATCH trial

- The NCI-MATCH study is an umbrella trial opened to multiple histologies (combination with basket): open to solid tumor or lymphoma patients who progressed on standard therapy, with plan to screen 6000 patients
- The study incorporates a custom DNA sequencing assay performed by a network of labs. Each treatment option has a set of rules mapping the biomarker and clinical information into a list of eligible treatments
- Each treatment is an independent single arm Phase II study with objective response rate as the primary outcome
- Primary endpoint: Objective response rate (ORR)

  H0: ORR = 5% vs. Ha: ORR > 5%
- Secondary endpoint: Progression-free survival (6 m)

Molecular Analysis for Therapy CHoice(MATCH): multi-arm basket trial

Signal finding study with master screening protocol directing to multiple biomarker-based (measured by NGS) mixed histology single arm phase II trial sub-protocols. (NCT02465060)



Opened in Fall 2015 with 10 treatment options

Co-developed by NCI and ECOG-ACRIN

Esercitazione sui tipi di studio

- Cohort study
- Randomized study
- Case-control study
- Real world study
- Disease registries

Association of Proton Pump Inhibitors (PPI) With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt,MD, PhD; Friederike Thome, MSc; Karl Broich, MD;Wolfgang Maier, MD; Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

PPI are used mainly to reduce gastric acid production

IMPORTANCE Medications that influence the risk of dementia in the elderly can be relevant for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases but have also been shown to be potentially involved in cognitive decline.

OBJECTIVE To examine the association between the use of PPIs and the risk of incidentdementia in the elderly.

DESIGN, SETTING, AND PARTICIPANTS We conducted a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK). Data on inpatient and outpatient diagnoses (coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and drug prescriptions (categorized according to the Anatomical Therapeutic Chemical Classification System) were available on a quarterly basis. Data analysis was performed from August to November 2015.

EXPOSURES Prescription of PPI: omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.
MAIN OUTCOMES AND MEASURES The main outcome was a diagnosis of incident dementia coded by the German modification of the *International Statistical Classification of Diseasesand Related Health Problems, Tenth Revision*. The association between PPI use and dementia was analyzed using time-dependent Cox regression. The model was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.
RESULTS A total of 73 679 participants 75 years of age or older and free of dementia at baseline were analyzed. The patients receiving regular PPI medication (n = 2950; mean [SD] age, 83.8 [5.4] years; 77.9%female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70 729; mean [SD] age, 83.0 [5.6] years; 73.6%female) (hazard ratio, 1.44 [95%CI, 1.36-1.52]; $P < .001$).
CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and is in line with mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice. Randomized, prospective clinical trials are
needed to examine this connection in more detail.

JAMA Neurol. 2016;73(4):410-416. doi:10.1001/jamaneurol.2015.4791

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley, MD; et al.for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

Context.—Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective.—To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.

Design.—Randomized, blinded, placebo-controlled secondary prevention trial.

Setting.—Outpatient and community settings at 20 US clinical centers.

Participants.—A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention.—Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and75% at the end of 3 years.

Main Outcome Measures.—The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results.—Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and10%higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (eachP,.001). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events and gallbladder disease. There were no significant differences in several other end points ……

Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

JAMA. 1998;280:605-613

Food Groups and Alcoholic Beverages and the Risk of Stomach Cancer: A Case-Control Study in Italy

E. Lucenteforte, et al.

To investigate the role of a wide range of foods and beverages on the risk of stomach cancer, we analyzed data from a case-control study carried out in Italy between 1997 and 2007 on 230 subjects with incident histologically confirmed stomach cancer (143 men and 87 women, age range 22–80 yr) and 547 controls (286 men and 261women, age range 22–80 yr) admitted to hospital for acute, non neoplastic diseases. Odds ratios (OR) of stomach cancer were estimated using unconditional multiple logistic regression models, adjusted for age, sex, energy intake, and other selected variables.

A direct association with stomach cancer risk was observed for cereals (OR=2.07, 95% CI = 1.01–4.24, for the highest compared to the lowest quintile of intake, *P* for trend = 0.03), soups (OR = 1.94, 95% CI = 1.10–3.42, *P* for trend = 0.05), and potatoes (OR = 2.04, 95% CI = 1.05–3.98, *P* for trend = 0.04). Conversely, inverse trends in risk were observed with vegetables (OR = 0.47, 95% CI = 0.27–0.81, *P* for trend = 0.01) and fruit intake (OR = 0.53, 95% CI = 0.30–0.93, *P* for trend = 0.08).

The results of this study confirm a protective role of vegetables and fruit against stomach cancer and suggest a detrimental effect of (refined) cereals on this neoplasm.

Nutrition and Cancer, 60(5), 577–584, 2008

Real world study comparing commonly prescribed COPD medicines shows choice of treatment has impact on patient outcomes

Tuesday, 19 March 2013

AstraZeneca today announced that an analysis of data from real world study PATHOS, published in the Journal of Internal Medicine, show that chronic obstructive pulmonary disease (COPD) patients treated with SYMBICORT® Turbuhaler® (budesonide/formoterol) are significantly less likely to suffer from COPD-related exacerbations – or 'flare ups' – and are significantly less likely to be hospitalised for COPD than those treated with SERETIDE™ (fluticasone/salmeterol).1 PATHOS is the largest real world study to compare the effectiveness of two commonly prescribed inhaled corticosteroid and long-acting beta agonist (ICS/LABA) combination treatments for COPD with more than one year of patient follow up.

Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study.

Larsson K, Janson C, Lisspers K, Jørgensen L, Stratelis G, Telg G, Ställberg B, Johansson - Karolinska Institutet, Stockholm, Sweden. kjell.larsson@ki.se

Abstract

OBJECTIVES: Combinations of inhaled corticosteroids (ICSs) and long-acting β2 - agonists (LABAs) are recommended for patients with moderate and severe chronic obstructive pulmonary disease (COPD). However, it is not known whether different fixed combinations are equally effective. The aim of this study was to investigate exacerbation rates in primary care patients with COPD treated with budesonide/formoterol compared with fluticasone/salmeterol.

METHODS: Patients with physician-diagnosed COPD and a record of postdiagnosis treatment with a fixed combination of budesonide/formoterol or fluticasone/salmeterol were included. Data from primary care medical records were linked to those from Swedish national hospital, drug and cause of death registers. Pairwise (1 : 1) propensity score matching was carried out at the index date (first prescription) by prescribed fixed ICS/LABA combination. Exacerbations were defined as hospitalizations, emergency visits and collection of oral steroids or antibiotics for COPD. Yearly event rates were compared using Poisson regression.

RESULTS: Matching of 9893 patients (7155 budesonide/formoterol and 2738 fluticasone/salmeterol) yielded two cohorts of 2734 patients, comprising 19 170 patient-years. The exacerbation rates were 0.80 and 1.09 per patient-year in the budesonide/formoterol and fluticasone/salmeterol groups, respectively (difference of 26.6%; $P < 0.0001$); yearly rates for COPD-related hospitalizations were 0.15 and 0.21, respectively (difference of 29.1%; $P < 0.0001$). All other healthcare outcomes were also significantly reduced with budesonide/formoterol versus fluticasone/salmeterol.

CONCLUSIONS: Long-term treatment with fixed combination budesonide/formoterol was associated with fewer healthcare utilization-defined exacerbations than fluticasone/salmeterol in patients with moderate and severe COPD.

A **cancer registry** is an information system designed for the collection, storage, and management of data on persons with cancer.

Registries play a critical role in cancer surveillance, which tells us where we are in the efforts to reduce the cancer burden. Surveillance data may also serve as a foundation for cancer research and are used to plan and evaluate cancer prevention and control interventions.