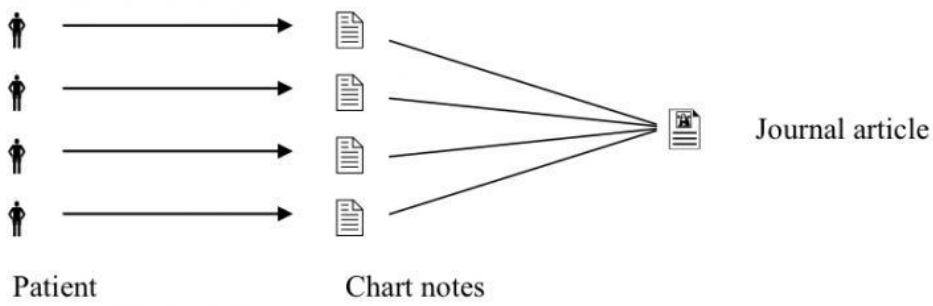
Design of studies and clinical trials and effect on outcome

Case Series and Case Reports

- Collections of reports on the treatment of individual patients
- Reports on a single patient
- Easy to understand, quick to write up

Jonathan Koffel University of Minnesota

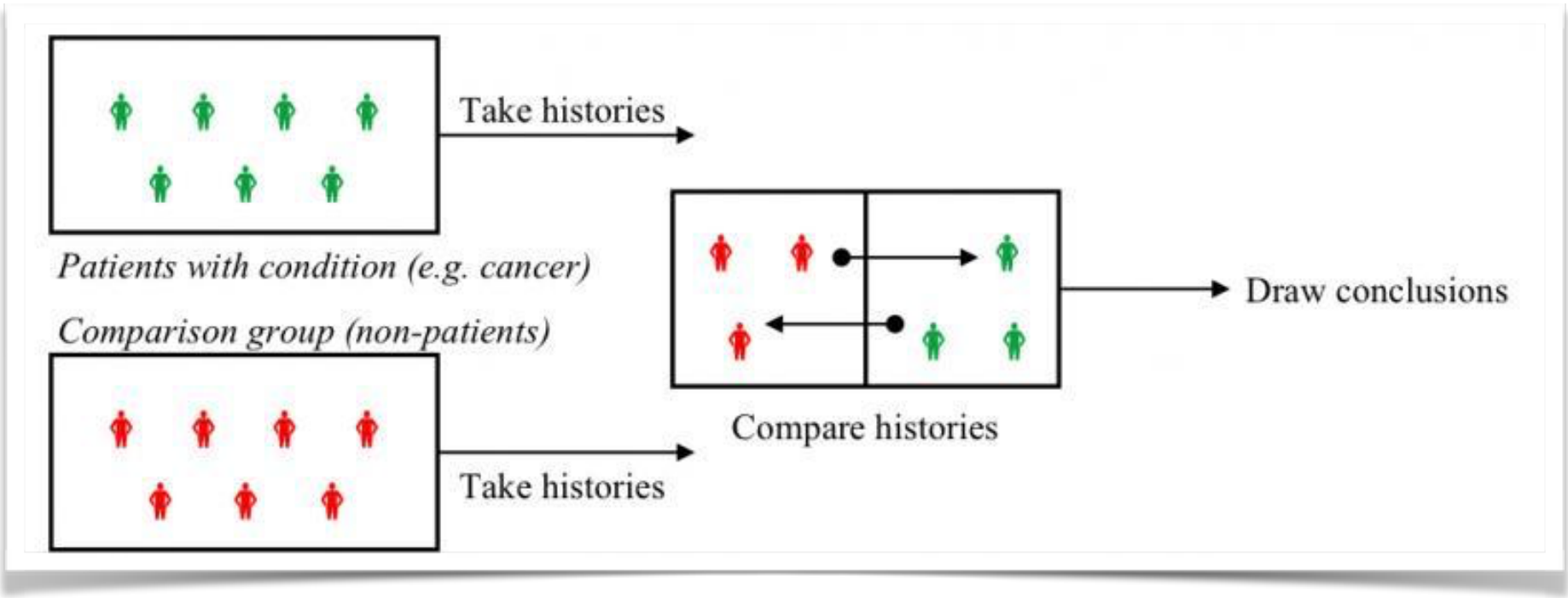


Case reports

- Characterise or illustrate aspect of a condition
  - Treatment
  - Adverse reaction
- No control group
- Anecdotal - no statistical validity

Case Control Studies

- Compare patients with a condition to those who do not have the condition
- Aim to estimate the odds (using an odds ratio) of developing the disease
- Determine if there is association between condition and risk factor



Colon cancer patients are asked what kinds of food they have eaten in the past and the answers are compared with a selected control group.

Attributes to outcome

- less reliable than randomized controlled trials or cohort studies
- cannot directly obtain absolute risk (incidence) of a bad outcome
- can be done quickly and are very efficient for conditions/diseases with rare outcomes

Cohort (longitudinal studies) Studies

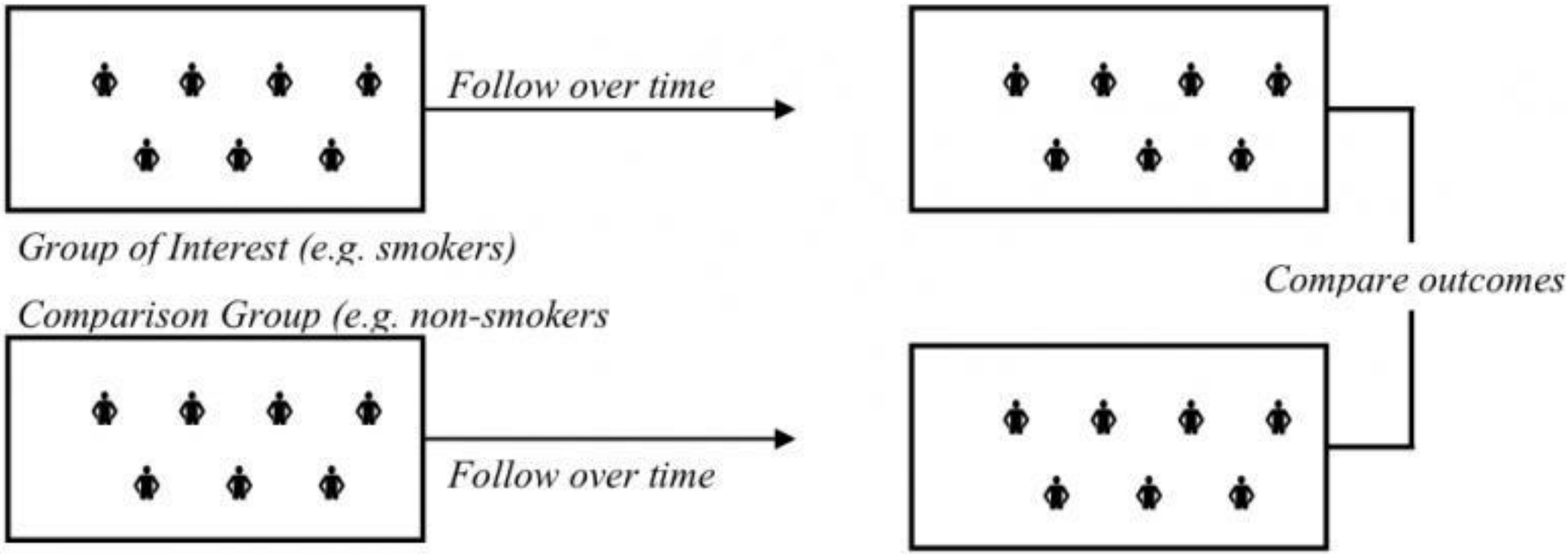
Case-defined population who presently have a certain exposure and/or receive a particular treatment that are followed over time and compared with another group who are not affected by the exposure under investigation

Types of cohort study

- Prospective
  - exposure factors are identified at the beginning of a study and a defined population is followed into the future
- Retrospective
  - past medical records for the defined population are used to identify exposure factors

Application

- Used to establish causation of a disease or to evaluate the outcome/impact of treatment
- Require a large sample size
- Inefficient for rare outcomes
- Take long periods of time
- Randomized studies preferable
    - Groups may differ in ways other than the



Framingham Heart study

ENGLISH BANGLA URDU

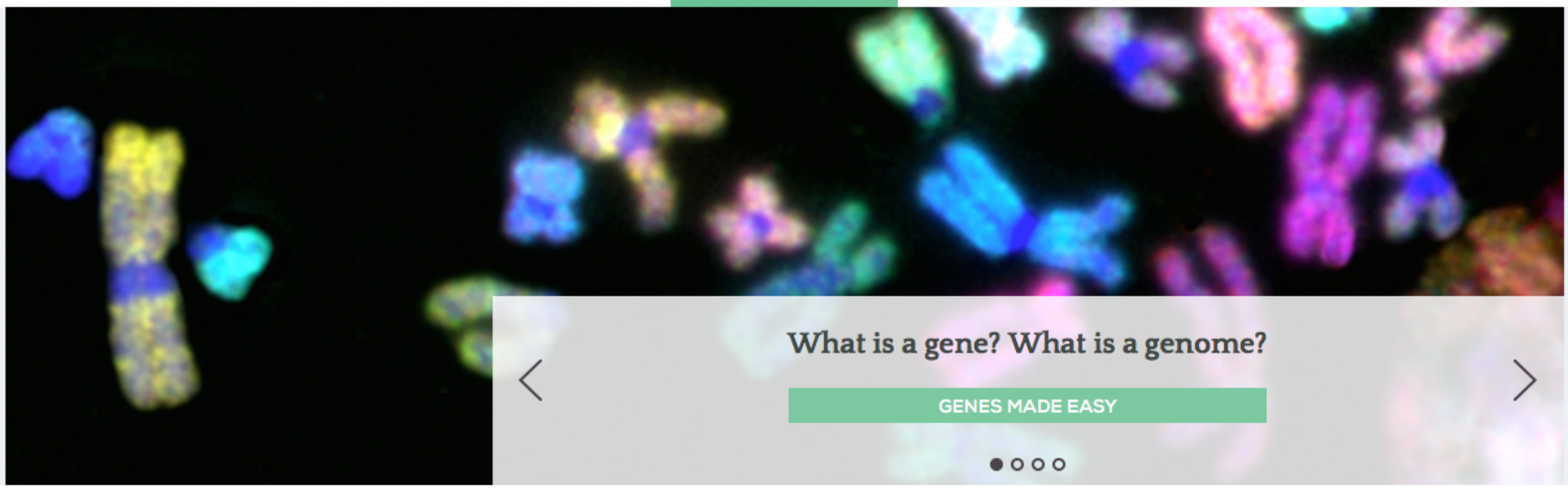
East London Genes & Health

Queen Mary University of London

Barts Health NHS NHS Trust

ABOUT THE STUDY • THE FIRST 46 • GENES & YOUR HEALTH • RESEARCH • NEWS & EVENTS • VOLUNTEER INFORMATION

VOLUNTEER NOW!



Improve health in East London

In East London, South Asian people have some of the highest rates of heart disease, diabetes, and poor health in the UK.

Genomics is changing healthcare

East London Genes & Health is one of the world's largest community-based genetics studies, aiming to improve health among people of Pakistani and Bangladeshi

Randomized Controlled Studies

- Two groups
  - one treatment group: receives the treatment under investigation
  - one control group: receives either no treatment (placebo) or standard treatment
- Random assignment to groups.

Attributes

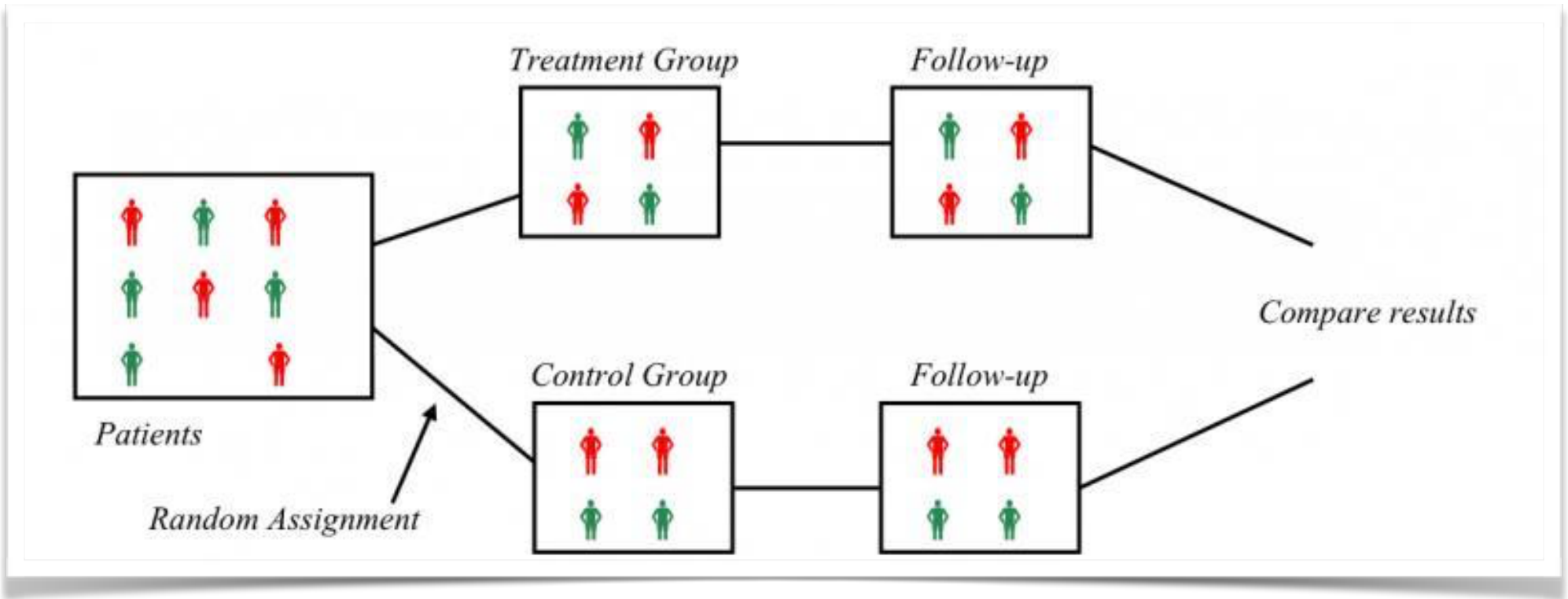
- Considered the "gold standard" in medical research.
- Answer questions about the effectiveness of different therapies or interventions
- Avoids bias in choice of patients-to-treatment that a physician might be subject to.
- Increases probability that differences between groups can be attributed to the treatment(s) under study.

Impact of control

- control group allows for a comparison of treatments
  - e.g., treatment A produced favorable results 56% of the time versus treatment B in which only 25% of patients had favorable results.

Ethics

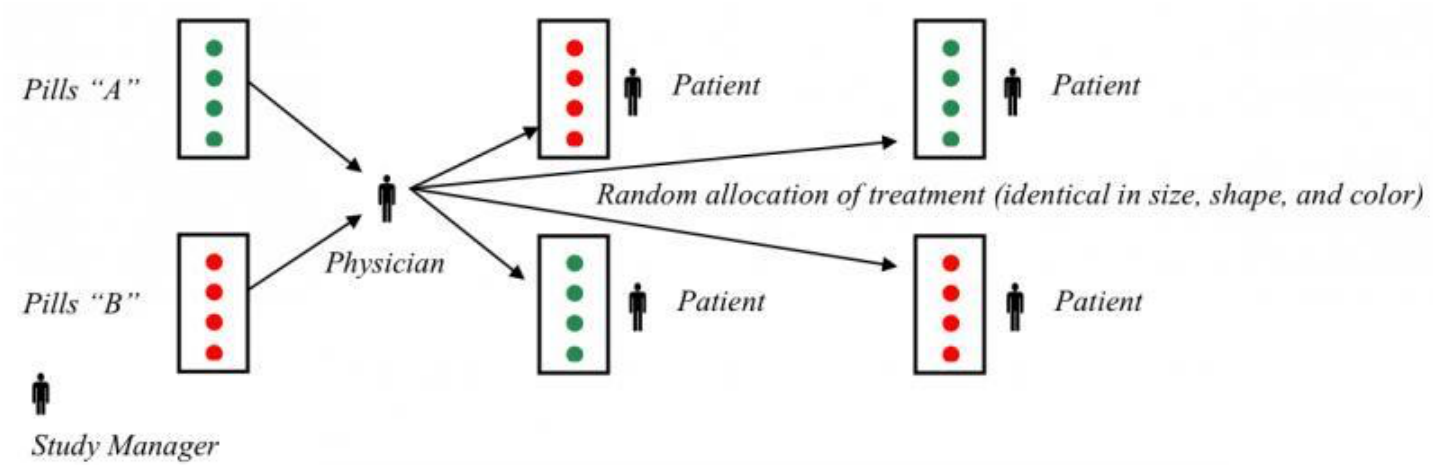
If patients asked to undertake harmful experiences (exposure to HIV virus) or denied treatment beyond a placebo when there are known effective treatments



Double-Blind

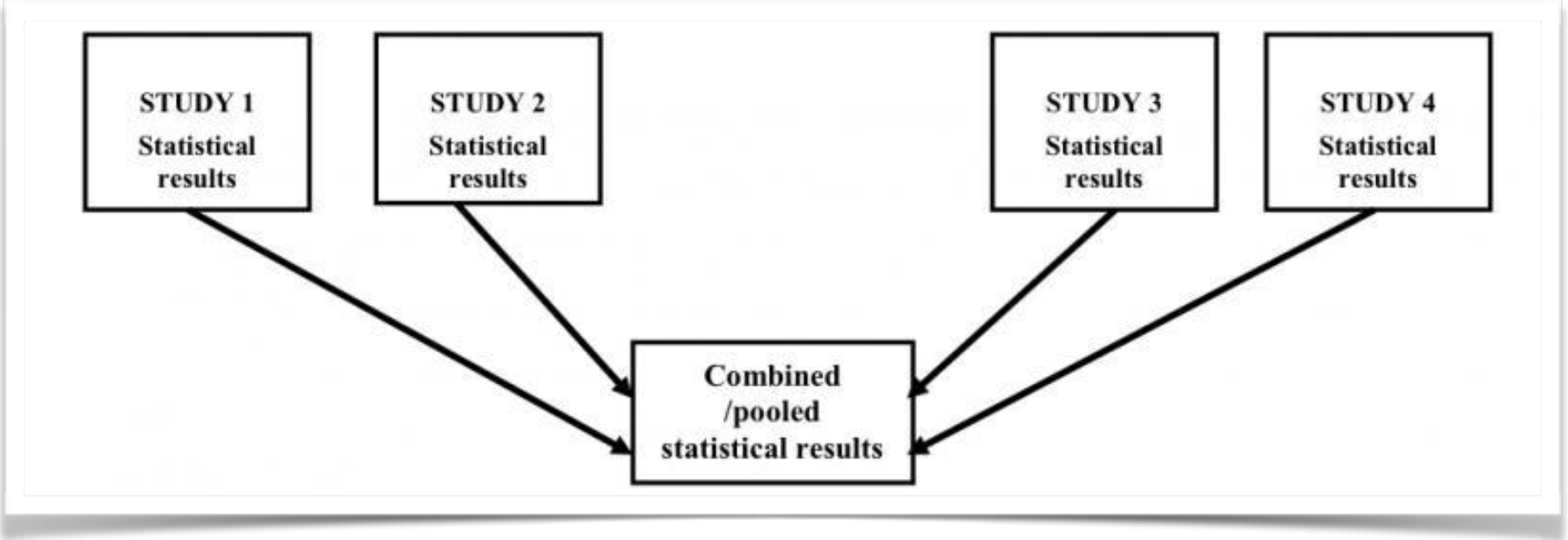
- Randomized controlled clinical trial
  - neither medical staff or patient knows which of several possible treatments is being provided

- patient takes one of two pills of identical size, shape, and color, and neither the patient nor the physician needs to know which is which
- rigorous clinical research design
  - randomization of subjects
    - reduces the risk of bias
    - minimize the placebo effect (validity of study)



Meta-Analyses

- Systematic, objective combination of data from many studies
  - Randomized controlled clinical trials
- Pooled estimate of treatment effectiveness together with statistical significance.



- Combine data from case/control and cohort studies.
  - Increases sample size
  - allows for analyses that would not otherwise be possible

Outcome affects

- Publication bias
  - no or little effect often not published
    - How many no effect trial results are published?
- Misleads results when all the data on the subject from “published” literature are summarised

Systematic Reviews

- Comprehensive survey of a topic that takes great care to find all relevant studies of the highest level of evidence
- more rigorous than a traditional literature review and attempts to reduce the influence of bias

systematic review

- published and unpublished studies
  - each study assessed consistently
  - synthesise findings from individual studies
  - unbiased
  - explicit
  - reproducible

Unreliable research: Trouble at the lab | The Economist 1/5/1

More from The Economist | Subscription | Log in or register

The Economist | World politics | Business & finance | Economics | Science & technology | Culture | Blogs | Debate | Multimedia | Print edition

This site uses cookies. By continuing to browse the site you are agreeing to our use of cookies. Review our cookies information for more details

Unreliable research

Trouble at the lab

Comment (199) Print

E-mail Reprints & perm

Scientists like to think of science as self-correcting. To an alarming degree, it is not

Oct 19th 2013 | From the print edition

Like Tweet

Jason Ford

"I SEE a train wreck looming," warned Daniel Kahneman, an eminent psychologist, in an open letter last year. The premonition concerned research on a phenomenon known as "priming". Priming studies suggest that decisions can be influenced by apparently irrelevant actions or events that took place just before the cusp of choice. They have been a boom area in psychology over the past decade, and some of their insights have already made it out of the lab and into the toolkits of policy wonks keen on "nudging" the populace.

Dr Kahneman and a growing number of his colleagues fear that a lot of this priming research is poorly founded. Over the past few years various researchers have made systematic attempts to replicate some of the more widely cited priming experiments. Many of these replications have failed. In April, for instance, a paper in *PLoS ONE*, a

Follow *The Economist*

Latest blog posts - All times are GMT

Marijuana legalisation: Sort of in de of David Brooks
Democracy in America - Jan 3rd, 23:29

Trouble at the Panama Canal: Your money or your locks
Americas view - Jan 3rd, 20:40

most published research findings are probably false

2005 John Ioannidis, Stanford

1 in 20 is level of significance

- findings ignore statistical power (small samples sizes, false negative missed in noise)
- unlikeliness of hypothesis
- bias to publish something new

Statistical power

- Able to pick things up even when their effects on the data are small
- bigger studies "run the experiment more times" recruit more patients for the trial are more powerful
- A power of 0.8 means that of ten true hypotheses tested, only two will be ruled out because their effects are not picked up in the data

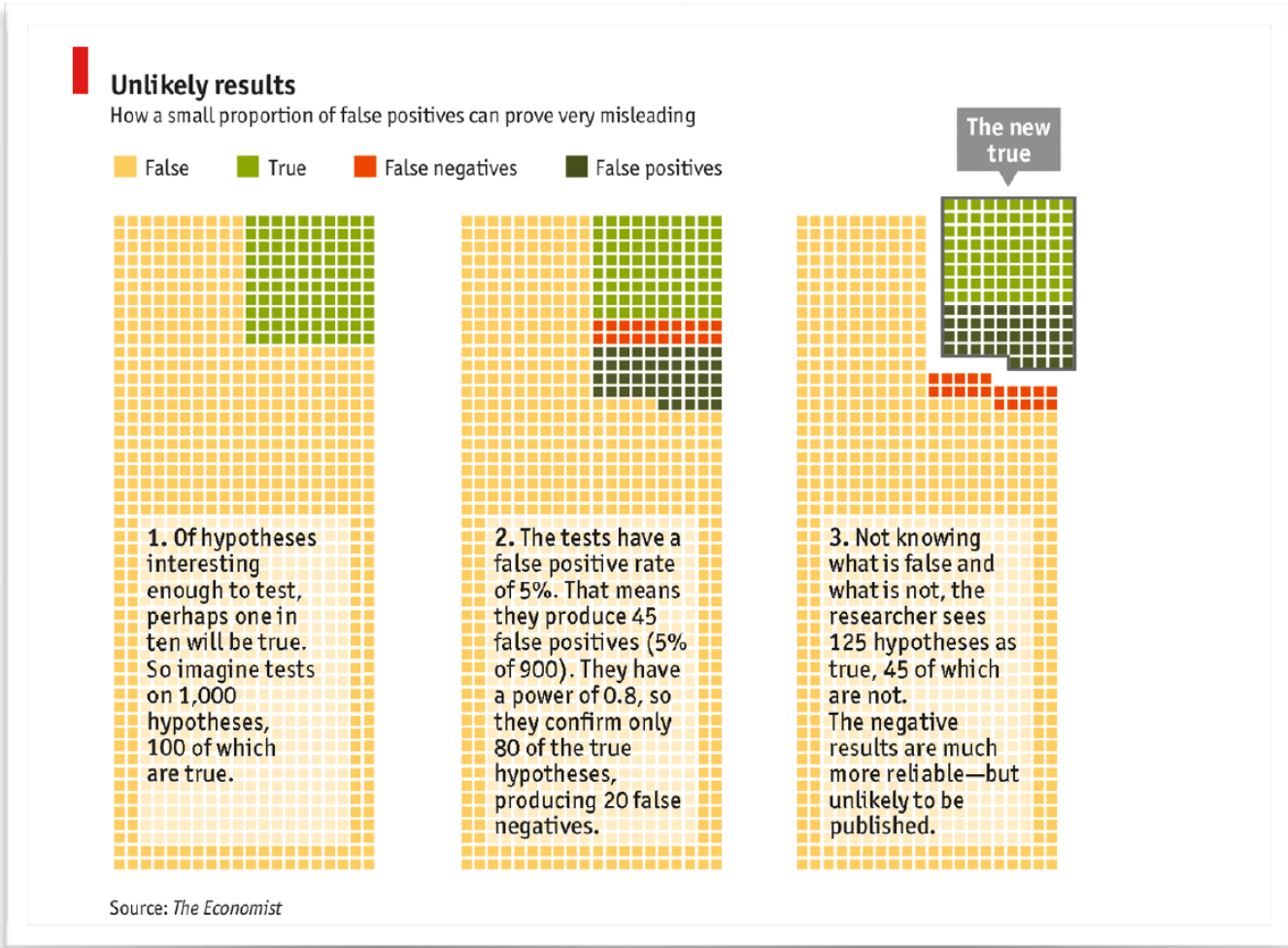
Neuroscience

- typical statistical power is 0.21
- overall 0.35

Marjan Bakker, Perspectives on Psychological Science

Genomics

- expect just one in a thousand to prove correct
- 1,000 hypotheses being tested of which just 100 are true



- balanced and impartial summary of the findings with due consideration of any flaws in the evidence
- evaluation of either existing or new technologies and practices

Bias and systematic review

- Clearly formulated research question
- Published & unpublished (conferences, company reports, "file drawer reports") literature is carefully searched for relevant research
- Identified research assessed by explicit methodology
- Results of the critical assessment of the individual studies are combined
- Final results are in context, addressing quality of the included studies, impact of bias and the applicability of findings
- Difference between a systematic review and a meta-analysis is that a systematic review looks at the whole picture (qualitative view), while a meta-analysis looks for the specific statistical picture (quantitative view).

Genomic study design

Power

- what is the chance that my experiment could detect a real event/effect/ difference in my samples? (at a given FP rate)
  - Traditional: do I have enough samples to see this difference?
    - the assay gives a result for most samples
  - Sequencing: am I sampling enough sequence for each sample to get a result?

Genotyping

- Genotyping chip:
  - – ~95% samples work
  - – ~99% loci work (for well–designed chip)
  - – ~99% yield of calls per sample
- Sequencing
  - coverage

Real life

- chip is binding DNA and "counting" by fluorescence intensity
- Not enough intensity, software won't make the call
- never see intermediate results - single molecular events
- mismatch to protocol - low signal poor outcome

Sequencing

- pile of reads across your SNP
- precise count of alleles observed
- need enough counts to know what's there
- counts vary by site
- 50 reads per site, but you have 5, still make some calls, but not much better than the chip did on 10% of the needed DNA

Considerations in experimental design

- reference genome and the appropriate tools
- Gene annotations
- Variant calls and resource bias
- Genetic or other maps
- Population bias
- check http://www.molecularevolution.org/molevolfiles/presentations/

Feedback: https://goo.gl/forms/938nR2f00sXWJaks2