

Personalized Medicine

Separating the Hope from the Hype

Stephen Senn



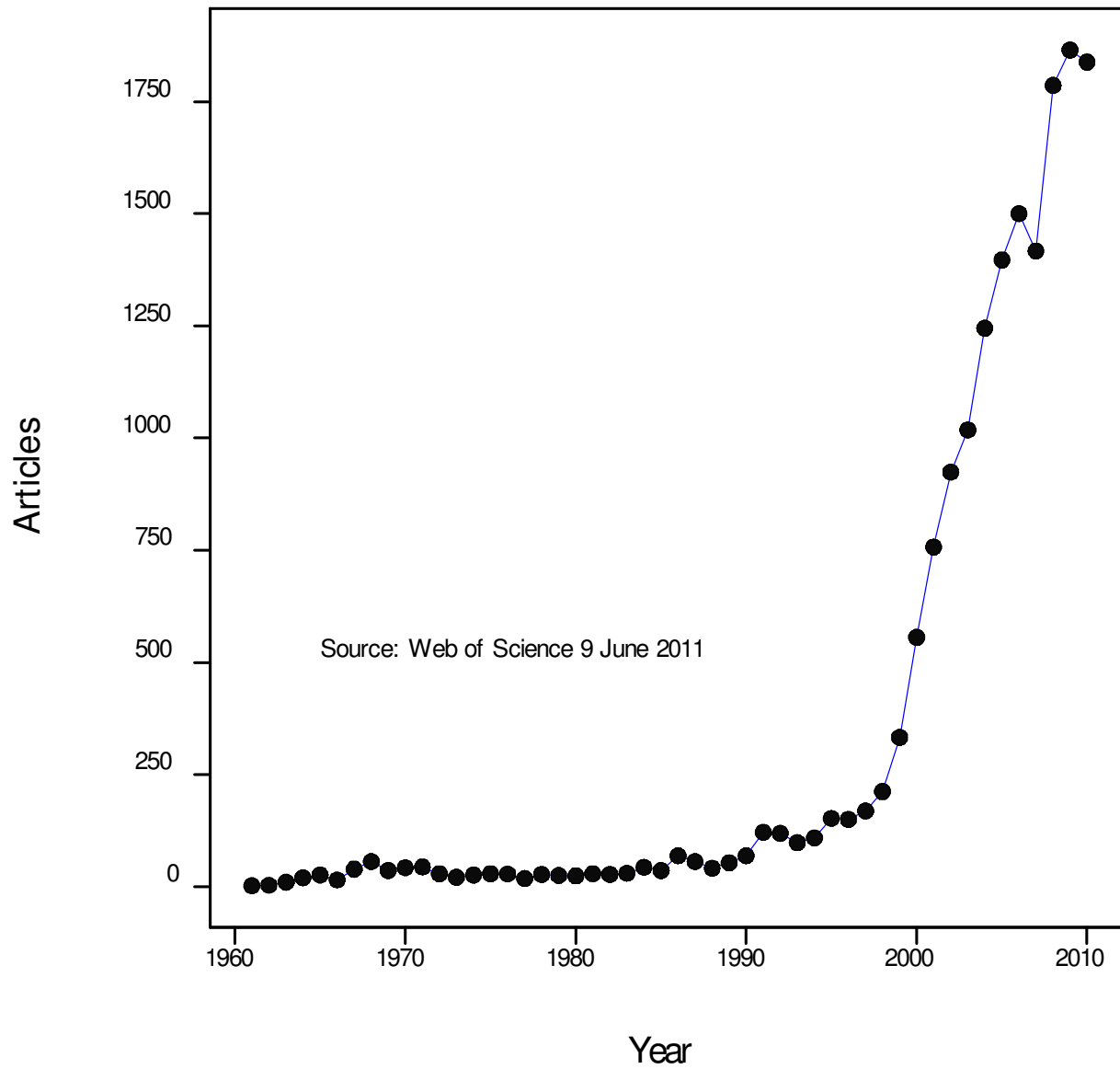
Genes, Means and Screens

It will soon be possible for patients in clinical trials to undergo genetic tests to identify those individuals who will respond favourably to the drug candidate, based on their genotype.... This will translate into smaller, more effective clinical trials with corresponding cost savings and ultimately better treatment in general practice. ... individual patients will be targeted with specific treatment and personalised dosing regimens to maximise efficacy and minimise pharmacokinetic problems and other side-effects.

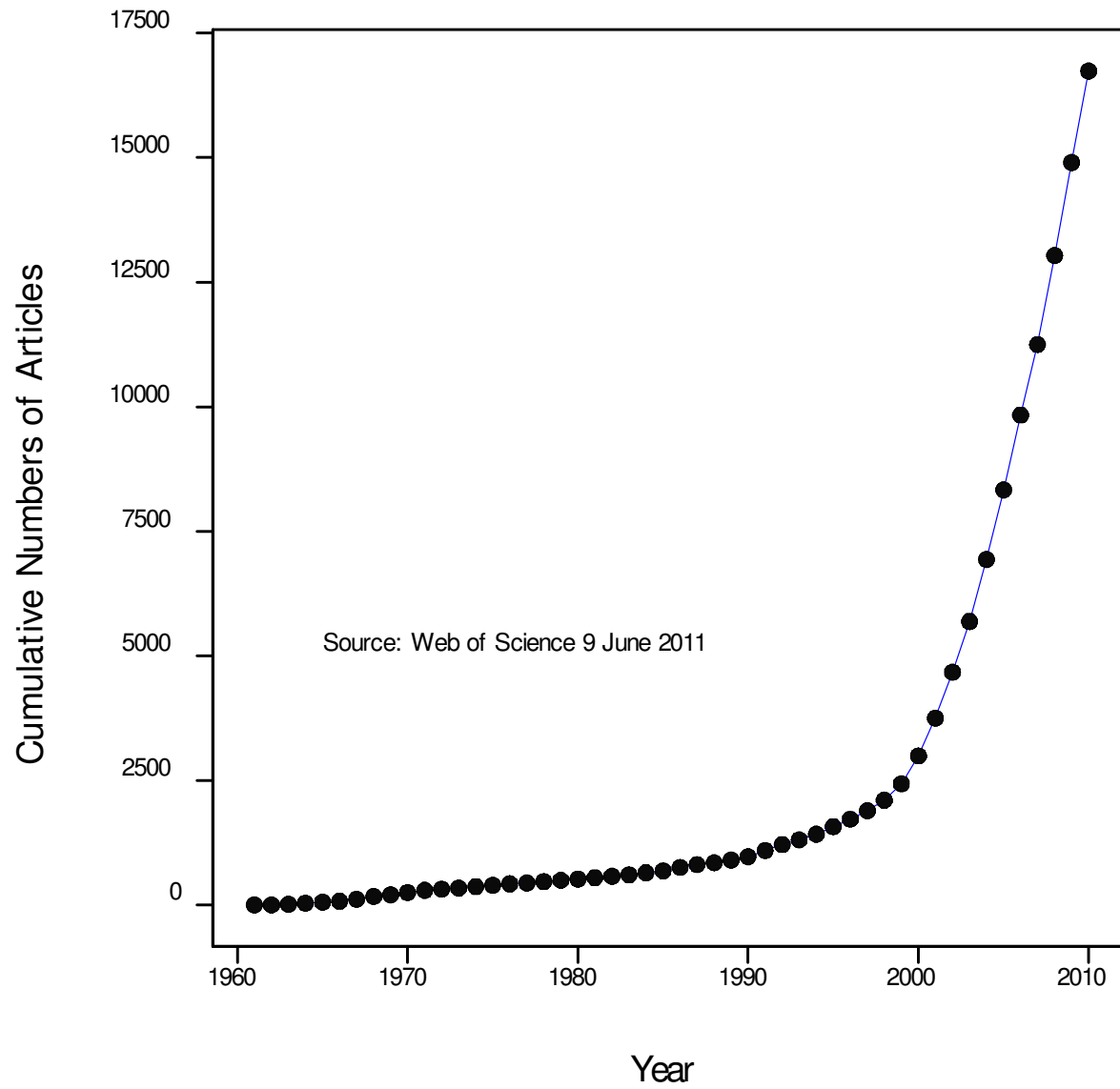
Sir Richard Sykes, FRS, 1997

Soon?

Articles on pharmacogenetics by publication year



Articles on pharmacogenetics by publication year



The Pharmacogenomic Revolution?

- Clinical trials
 - Cleaner signal
 - Non-responders eliminated
- Treatment strategies
 - “Theranostics”
- Markets
 - Lower volume
 - Higher price per patient day

Implicit Assumptions

- Most variability seen in clinical trials is genetic
 - Furthermore it is not revealed in obvious phenotypes
 - Example: height and forced expiratory volume (FEV_1) in one second
 - Height predicts FEV_1 and height is partly genetically determined but you don't need pharmacogenetics to measure height
- We are going to be able to find it
 - Small number of genes responsible
 - Low (or no) interactive effects (genes act singly)
 - We will know where to look
- In fact we simply don't know if most variation in clinical trials is due to individual response let alone genetic variability

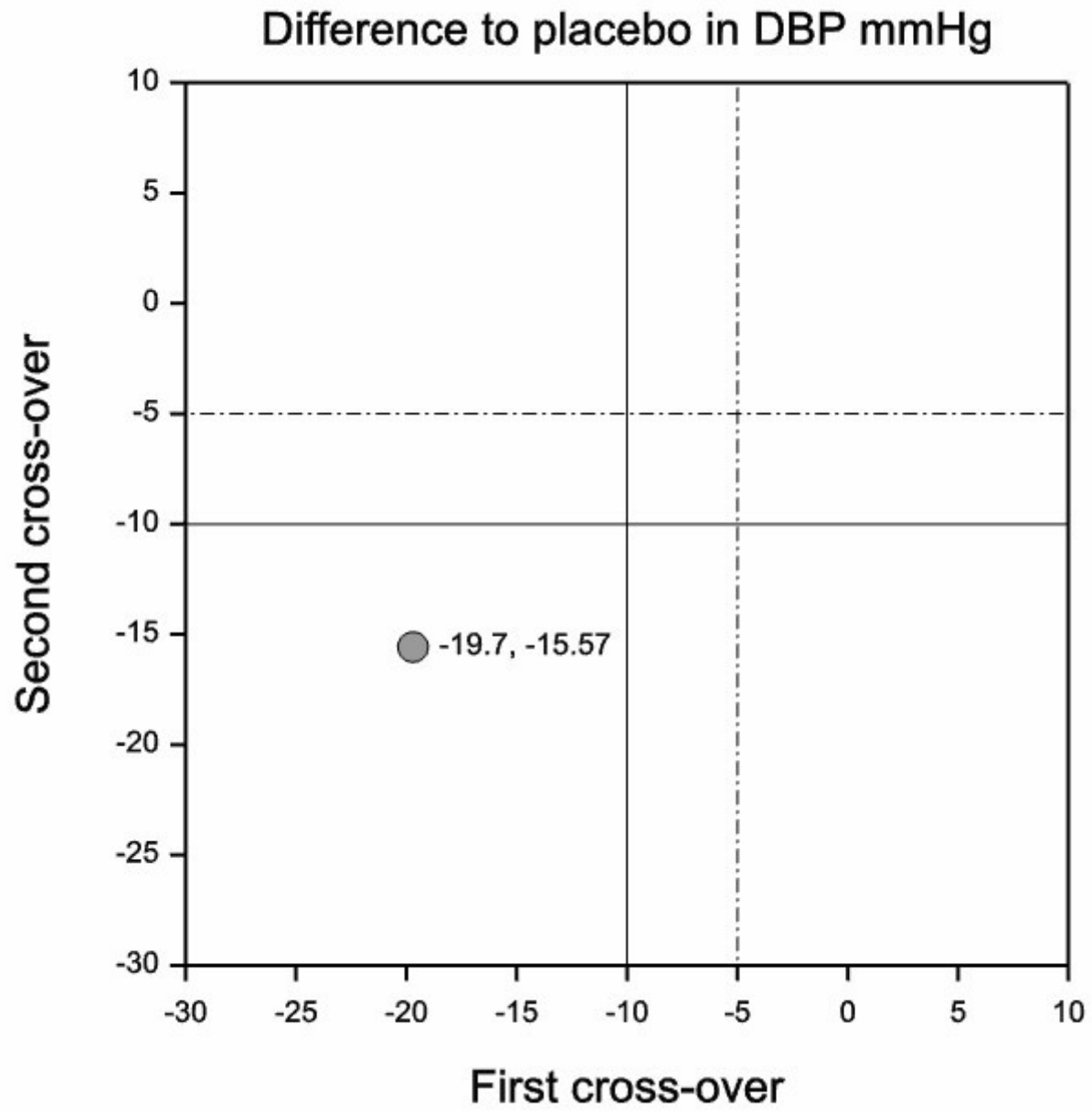
A Thought Experiment

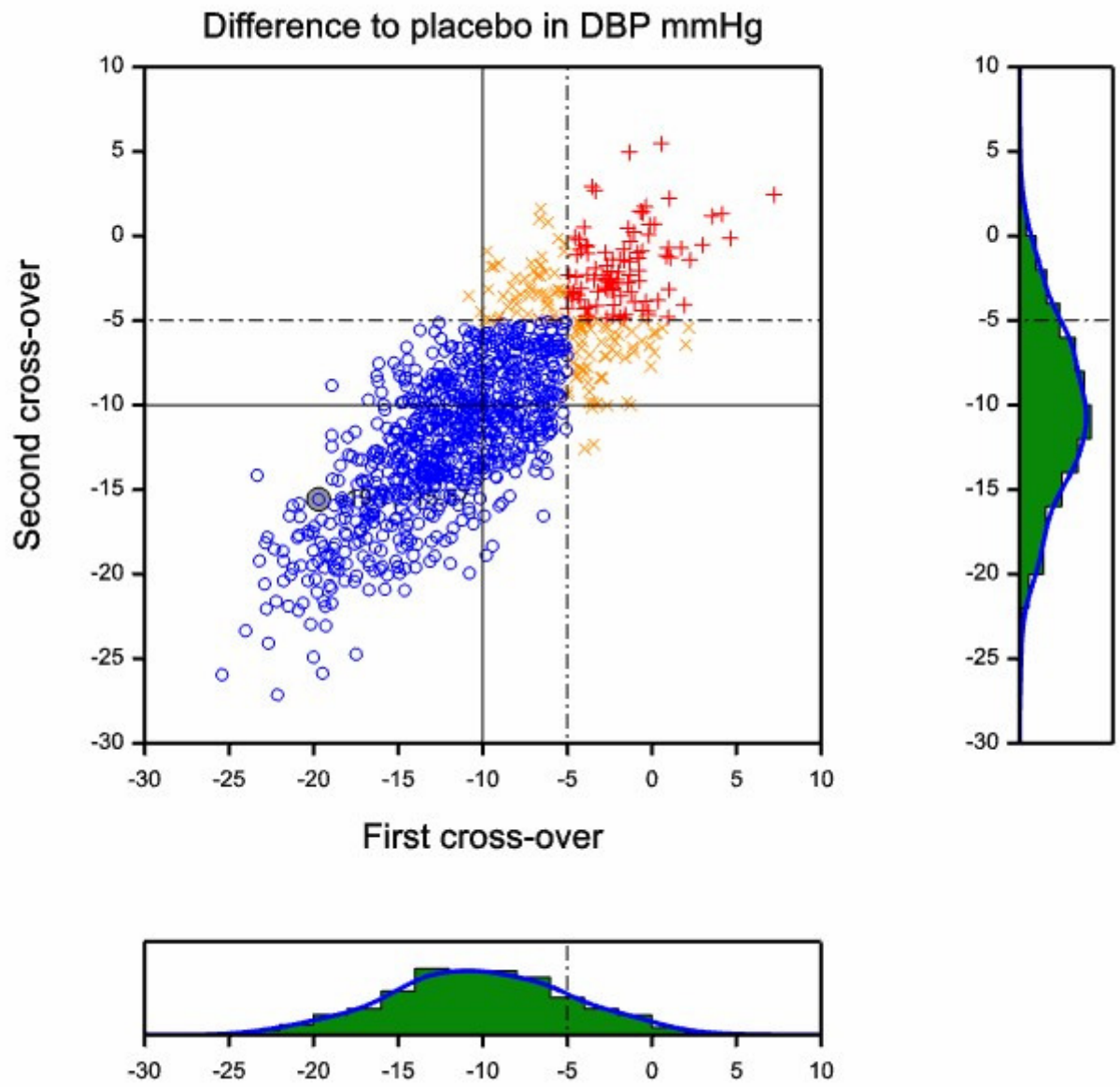
- Imagine a cross-over trial in hypertension
- Patients randomised to receive ACE II inhibitor or placebo in random order
- Then we do it again
- Each patient does the cross-over twice
- We can compare each patient's response under ACE II to placebo twice

Design

	First Cross-over		Second Cross-over	
	Period			
Sequence	1	2	3	4
I	A	B	A	B
II	B	A	B	A
III	A	B	B	A
IV	B	A	A	B

Each patient provides two estimates of the effect of B compared to A.
Once from periods 1 and 2.
Once from periods 3 and 4.





Results 1

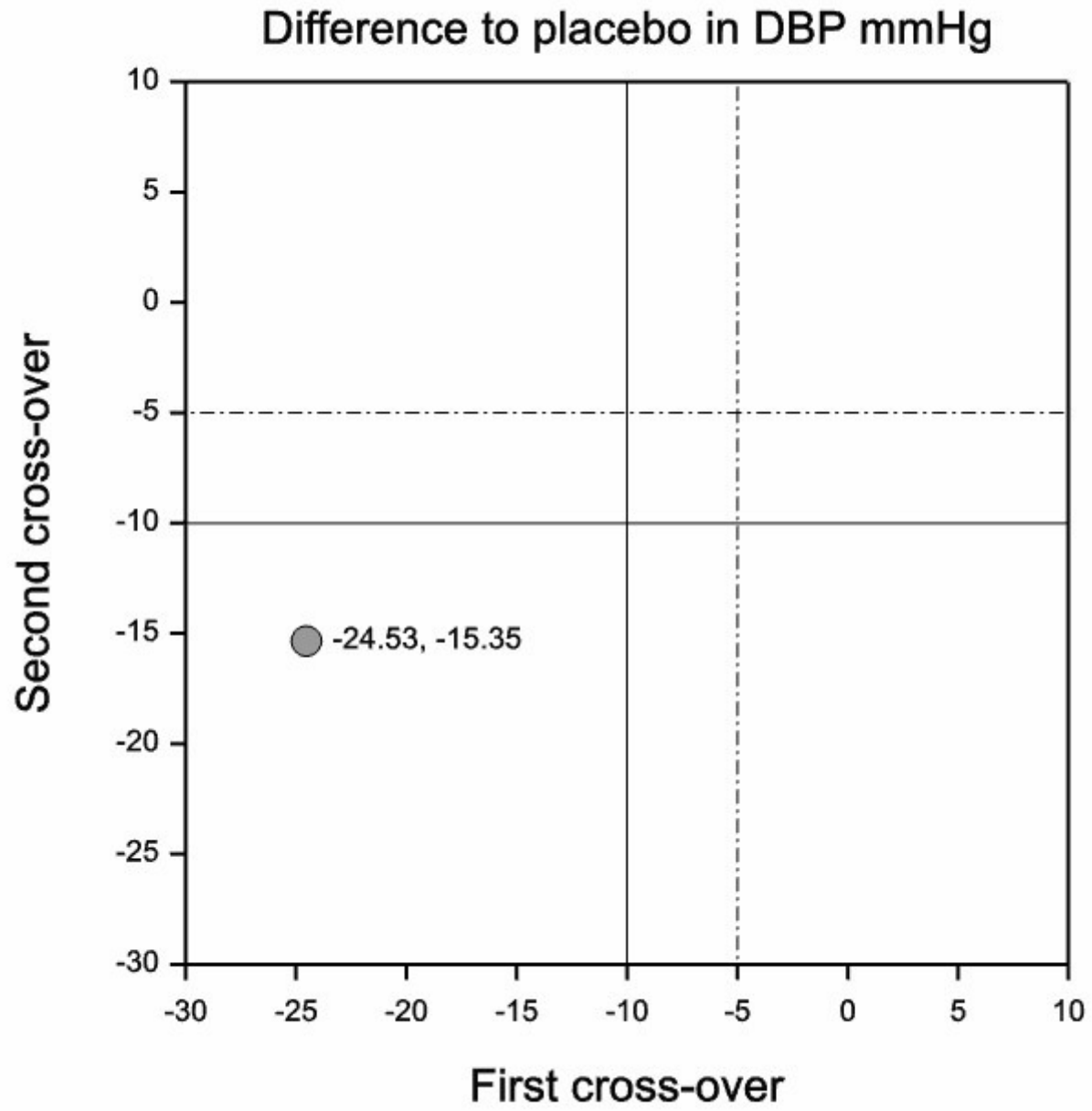
	Second Crossover			
		Responder	Non-responder	Total
First Cross-over	Responder	781	57	838
	Non-responder	66	96	162
	Total	847	153	1000

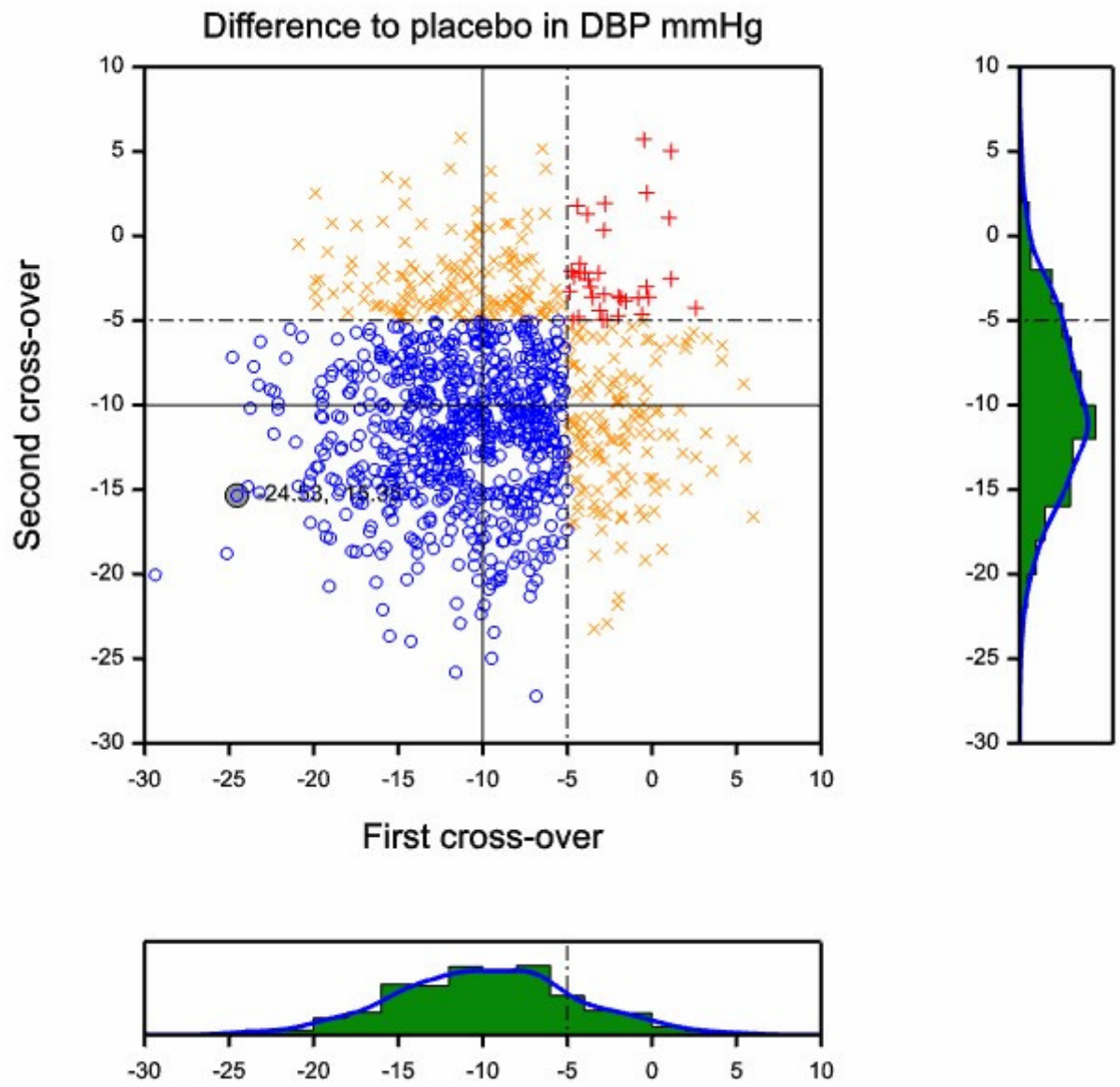
Correlation coefficient is
0.8

Conditional probabilities
of observed 'response'

$$\frac{781}{838} = 0.93$$

$$\frac{66}{162} = 0.41$$





Results 2

	Second Crossover			
		Responder	Non-responder	Total
First Cross-over	Responder	678	148	826
	Non-responder	140	34	174
	Total	818	182	1000

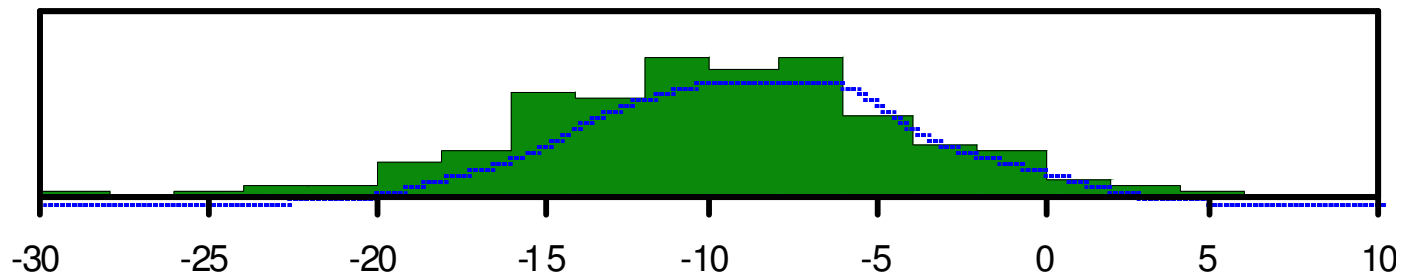
Correlation coefficient is
0.02

Conditional probabilities
of observed 'response'

$$\frac{678}{826} = 0.82$$

$$\frac{140}{174} = 0.80$$

?



Dichotomania

- Continuous measurements taken and referred to baseline
- Patients dichotomised as responder/non-responder
 - Inefficient
 - Arbitrary
 - Sheep versus goats
 - Ignores geep and shoats
- Analysis on risk difference scale to calculate NNT

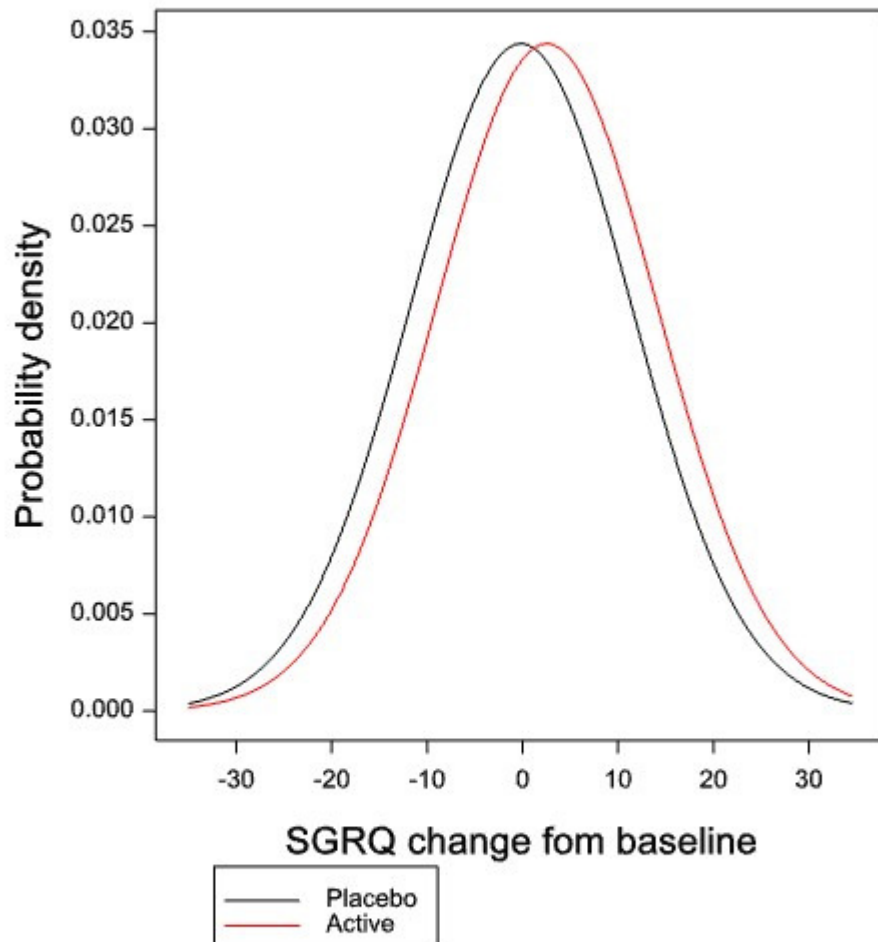
Pharmacogenetics: A cutting-edge science that will start delivering miracle cures the year after next.

Tiotropium v Placebo in Chronic Obstructive Pulmonary Disease

From the UPLIFT Study, *NEJM*, 2008

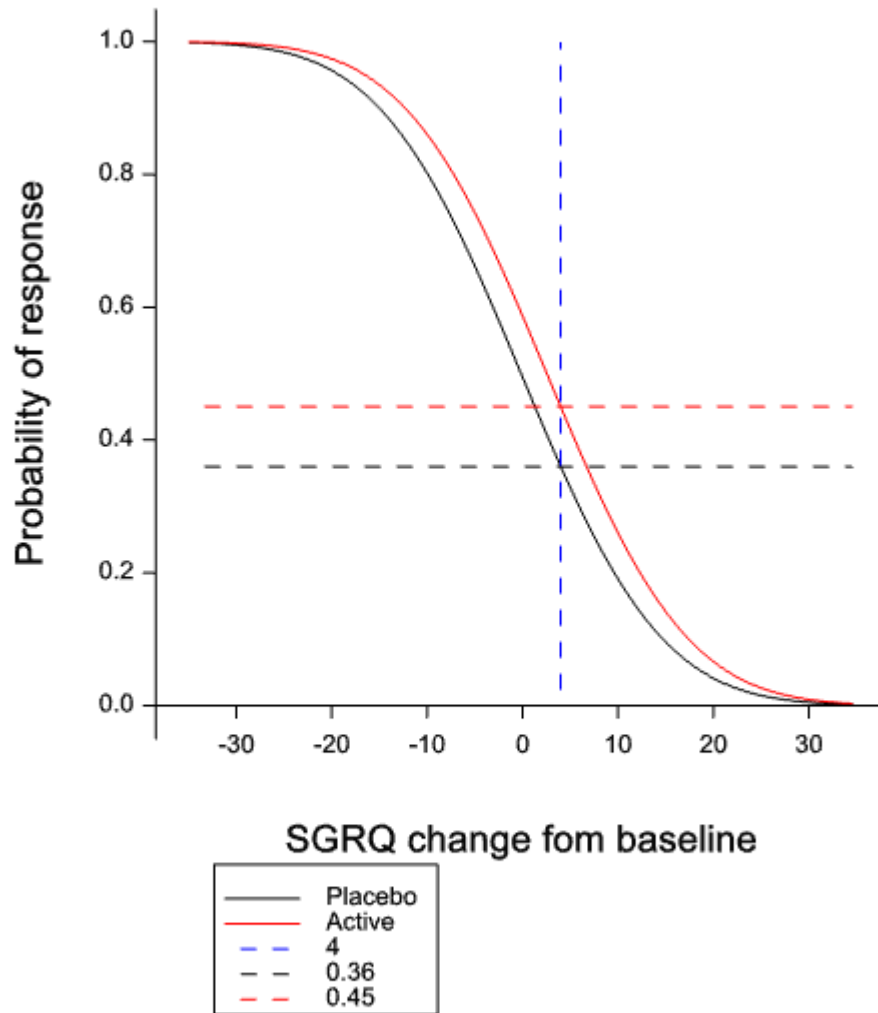
Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (ranging from 2.3 to 3.3 units, $P < 0.001$), although the differences on average were below what is considered to have clinical significance (Fig. 2D). **The overall mean between-group difference in the SGRQ total score at any time point was 2.7 (95% confidence interval [CI], 2.0 to 3.3) in favor of tiotropium ($P < 0.001$).** **A higher proportion of patients in the tiotropium group than in the placebo group had an improvement of 4 units or more in the SGRQ total scores from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%) ($P < 0.001$ for all comparisons).**

(My emphasis)



Two Normal distributions with the same spread but the Active treatment has a mean 2.7 higher.

If this applies every patient under active can be matched to a corresponding patient under placebo who is 2.7 worse off



A cumulative plot corresponding to the previous diagram.

If 4 is the threshold, placebo response probability is 0.36, active response probability is 0.45.

In summary...this is rather silly

- If there is sufficient measurement error even if the true improvement is identically 2.7, some will show an ‘improvement’ of 4
- The conclusion that there is a higher proportion of *true* responders *by the standard of 4 points* under treatment than under placebo is quite unwarranted
- So what is the point of analysing ‘responders’?

Who are the authors?

1. Tashkin, DP, Celli, B, Senn, S, Burkhardt, D, Kesten, S, Menjoge, S, Decramer, M. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease, *N Engl J Med* 2008.

Personal note. I am proud to have been involved in this important study and have nothing but respect for my collaborators. The fact that, despite the fact that two of us are statisticians, we have ended up publishing something like this shows how deeply ingrained the practice of responder analysis is in medical research. We must do something to change this.

In conclusion

- Responder analysis is the source of much confusion
- It is leading trialists to overestimate the individual element of response to treatment
- The key to understanding response is replication and careful analysis
- Stupid dichotomies do not help this understanding
 - NNTs may be relevant at the point of application but they are not relevant at the point of study
- Personalised medicine may be about to happen 'soon' for quite a few years to come yet