



Unzipping genomes and the public purse - science and society collide

Never Stand Still

Medicine

Prince of Wales clinical school and Lowy cancer research centre

Professor Robyn Ward

Director POW Cancer centre, Clinical Associate Dean UNSW

Chair of Medical Services Advisory Committee and Member PBAC



ADULT CANCER PROGRAM



**LOWY
CANCER
RESEARCH
CENTRE**

2001 - Human genome unzipped then cheap sequencing

- for a small fee our destiny is revealed
- transformational impact on well-being
- personalised treatment

And

It will save the healthcare budget of Western
countries

Selling the dream to the public/politicians

- Dramatic stories - exemplars are always more powerful than statistics
- Experts use anecdotes or testimonies
- Presentation of science as a black box



Selling the dream to scientists /journal editors/doctors

Appeal to our natural mode of thinking

- 1) Make a decision on emotional reasons
- 2) Develop a rational line of argument to fit the decision

Bypass scientific scepticism - rational filter through which all claims for truth must pass



Case studies of collisions between science (EBM) and society (values)

1. Drawing a bullseye after the arrow is fired



2. Cherry picking - notice only the things
which confirm our beliefs



3. Drunken walk of randomness

Case 2 - cherry picking



Targeted therapy for lung cancer

In a small group delays progression of disease by 4 months, but modelled benefit shows the drug delivers <20 days of perfect health

If the molecular testing is wrong the patient is harmed by the drug and is denied standard care, their disease will progress three months faster than it would have otherwise

i.e. One view is that the drugs add almost nothing to the treatment of lung cancer despite predicted annual cost of ~\$25Million

Observations



Firmly held beliefs determine :

- the things we notice
- attribution of value

And ultimately the conclusions we draw

Case 3 - Drunken walk of randomness



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Sunitinib Malate for the Treatment of Pancreatic
Neuroendocrine Tumors

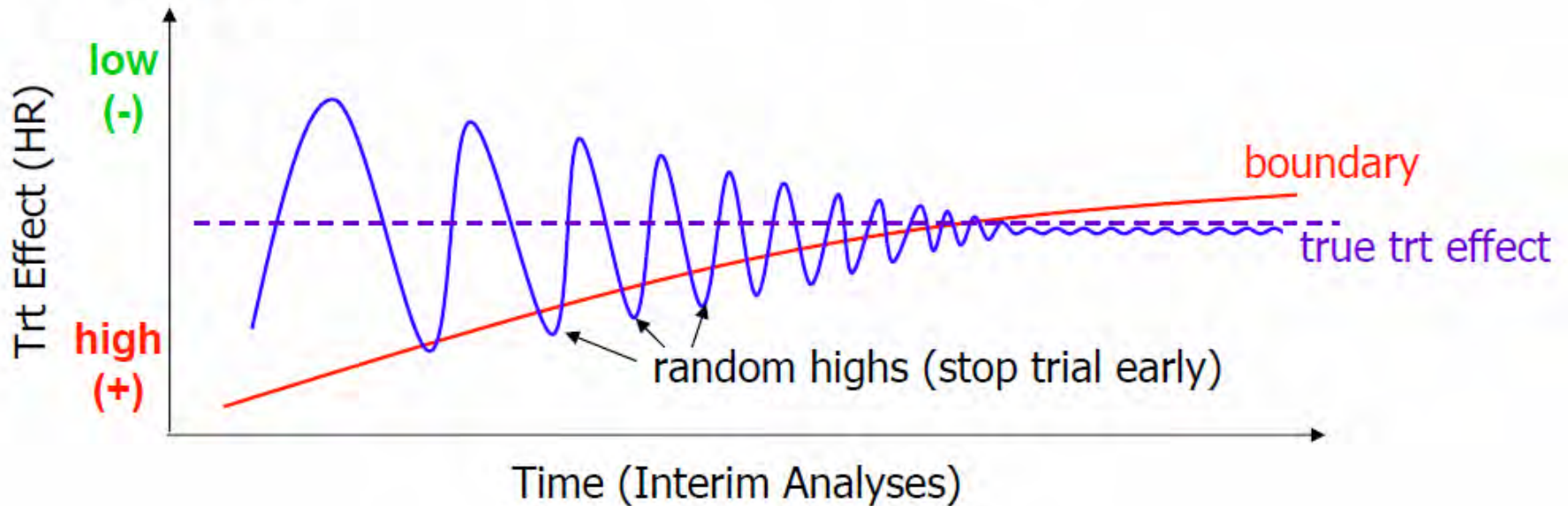


Sunitinib trial - analysis by FDA

- Three unplanned interim analyses
- Stopped the study early with 73 events observed (ie 28% of the expected events)
- Concordance in PFS between investigator and central radiologist was 57%
- Improper handling of missing assessments
- Improper use of progression criteria in 11.7% of patients



- GSDs**



DSM committee stopped study at 73 events (HR 0.397)
Study stopped at 81 events (HR 0.418)



Overestimation of benefit

“ .. A trial terminated early for benefit will tend to overestimate true effect; this happens because there is always **variability** in estimation of the true effect, and when assessing data over time, evidence of extreme benefit is more likely obtained at times when the data provide a **random** overestimation of truth”

Ellenberg, et al JAMA, 2010

Fortunately for sunitinib.....

It was a new targeted therapy

AND

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic
Neuroendocrine Tumors



Editorial NEJM



Promising Advances in the Treatment of Malignant Pancreatic Endocrine Tumors

Robert T. Jensen, M.D., and Gianfranco Delle Fave, M.D.

Severe disease

Chemotherapy ineffective

**Optimism created by the study results, both NEW
drugs are effective**



Observations



- Editorial did not mention of the issues with the conduct and analysis of the Sunitinib trial
- Missed opportunity to highlight the potential for overestimation of benefit
- Missed opportunity to explain that effect sizes of these drugs will likely decline over time because of regression to the mean

Conclusion

