Benefit-Risk modelling of pharmaceuticals: Where are we going?

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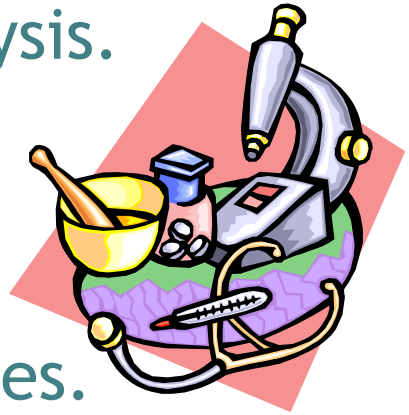
What is the industry doing?

Some companies apply quantitative modelling to...

- Screen leads in early Stage II to find the most promising leads for further development.
- Monitor the benefit-risk balance as new findings change the product profile.
- Screen compounds to decide which are ready to be entered into the annual portfolio analysis.
- Establish priorities for investing in drugs under development by carrying out portfolio analysis that identifies the most promising candidates.



What are regulators doing?

No regulator is able to consider a quantitative model in support of a new-drug application. But…

- The EMA is piloting the Effects Table for incorporating it in the Benefit-Risk section of the assessment reports by the Rapporteurs and CHMP.
- The FDA is beginning to use a qualitative approach that purports to be decision-analytic: see the talk by Patrick Frey at http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm298136.htm)
- Regulators are working behind the scenes to establish qualitative ICH B-R Guidelines

What are others doing?

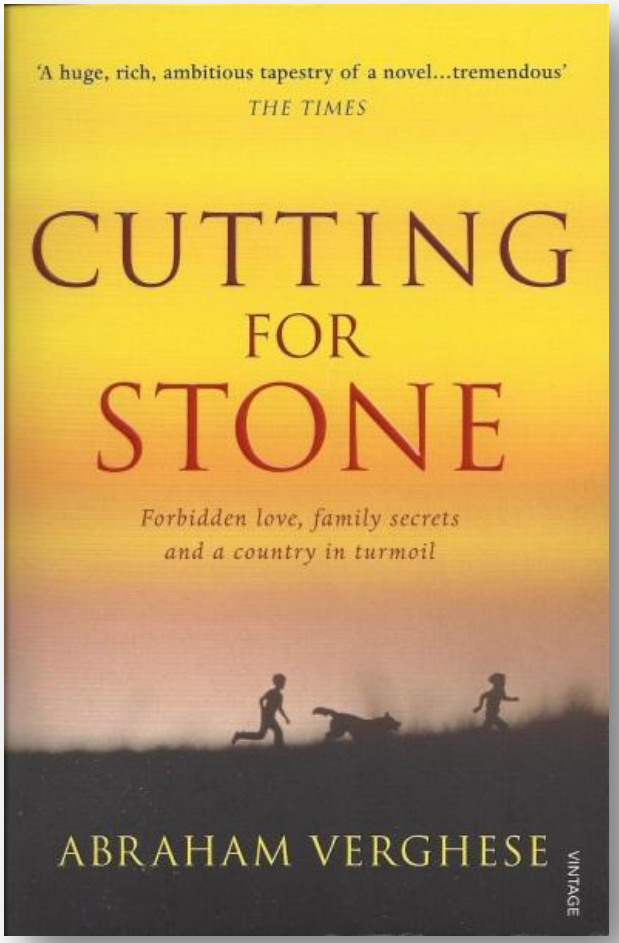
- The DIA has established a new Working Group on Benefit-Risk Assessment, as part of the Clinical Safety and Pharmacovigilance SIAC (Special Interest Area Communities).
- The Centre for Innovation in Regulatory Science (CIRS) has engaged in several activities under the UMBRA (Unified Methodologies for Benefit Risk Assessment) initiative (cirsci.org).
- Innovative Medicines Initiative (IMI) is funding the PROTECT project, a multi-national consortium of 33 partners, coordinated by the EMA and GSK. Work Package 5 is developing innovative approaches to B-R. (http://www.imi-protect.eu/)

Why has the medical profession been so slow in adopting quantitative decision support systems?

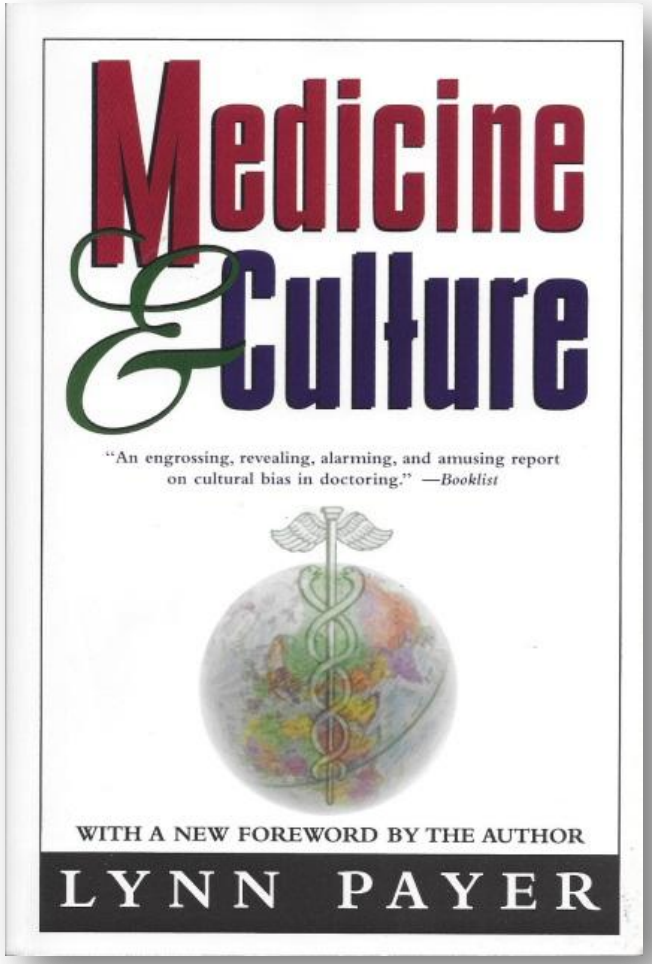
Words, not numbers

The novel's narrator, Marion Stone, as a boy, is learning medicine from his mentor, Ghosh, whose office contains medical textbooks :

"I found that the bricks and mortar of medicine (unlike, say, engineering) were words. You needed only words strung together to describe a structure, to explain how it worked, and to explain what went wrong."



Benefit-Risk depends on culture



"While scientifically conducted studies can show us that a certain course of action or treatment can result in certain benefits and risks, the weighing of those benefits and risks will always be made on a cultural scale." (p. 154)

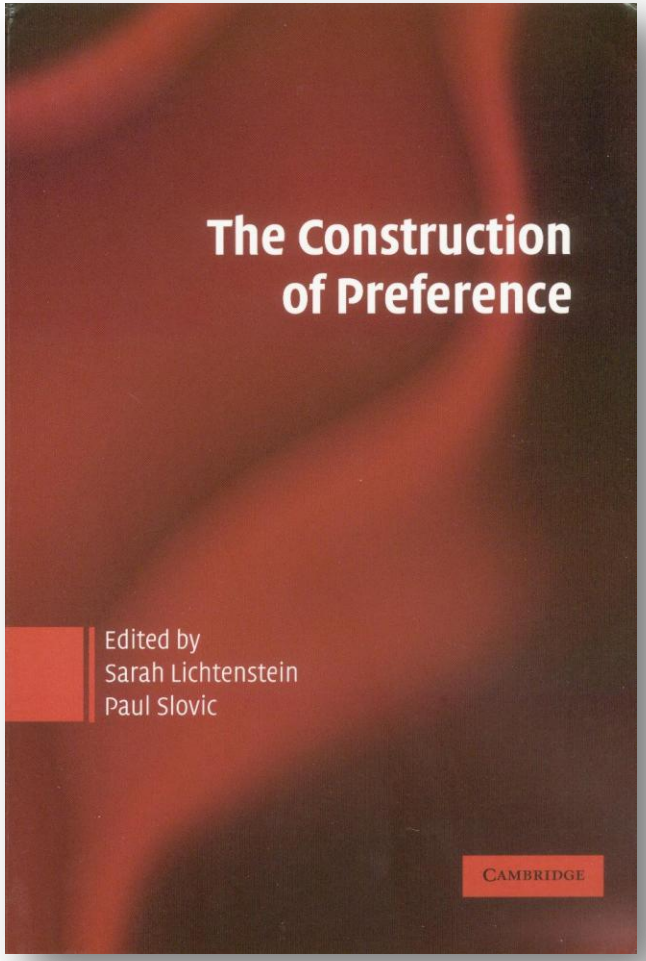
Bias to evidence-based decisions

" While medical ethicists and some enlightened doctors are beginning to see the large role value judgments play in medicine and realize that this implies a larger role for the patient in the making of medical decisions, most doctors, of course, continue to hide behind the screen of "scientific" medicine that somehow takes precedence over "unscientific" patient desires."

(Payer, pp. 154-155)

Value judgements can be more effective than objective measures.

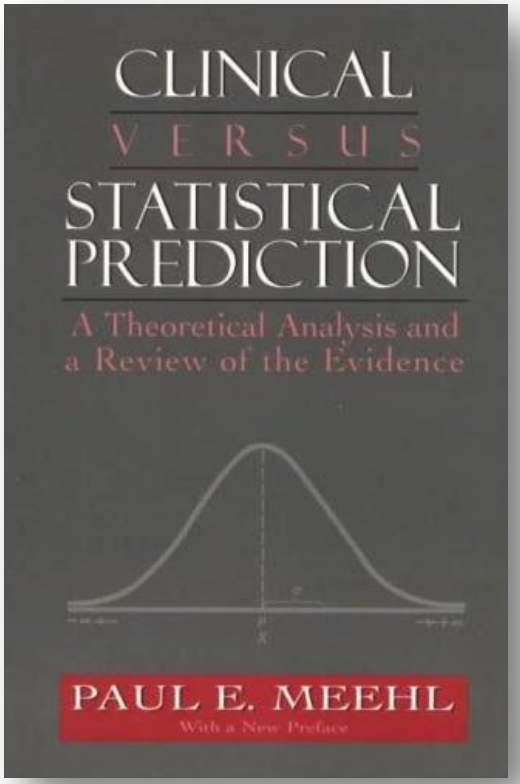
Models threaten authority



- Physicians gain authority by holding information relevant to a decision.
- However, decisions are based on preferences, which are formed by information *and* the decision maker's values.
- Models based on decision theory make explicit the data/values difference.
- Thus, these models pose a serious question: Who has the authority to impose values on any medical decision?

Overconfidence in judgement

- Meehl's 1954 book dropped a bombshell in clinical psychology.
- His survey of studies showed that simple, linear, additive models consistently out-perform clinical predictions of behaviour.
- He identified integration of multiple pieces of data as the problem, not the judgements about the pieces.
- By 1996, of 136 comparative studies, just 8 favoured clinical prediction.



Grove, W. M., & Meehl, P. E. (1996). Comparative efficiency of informal (subjective, impressionistic) and formal (mechanical, algorithmic) prediction procedures: The clinical-statistical controversy. *Psychology, Public Policy, and Law, 2, 293-323.*

What's next?

- Leadership for quantitative benefit-risk assessment will be mainly in the hands of the pharmaceutical industry.
- Regulators will work behind the scenes to change the culture from "implicit to explicit" and from "qualitative to quantitative".
- Universities and research centres will continue to provoke the industry and regulators to adopt state-of-the-art methodologies.

THANK YOU!