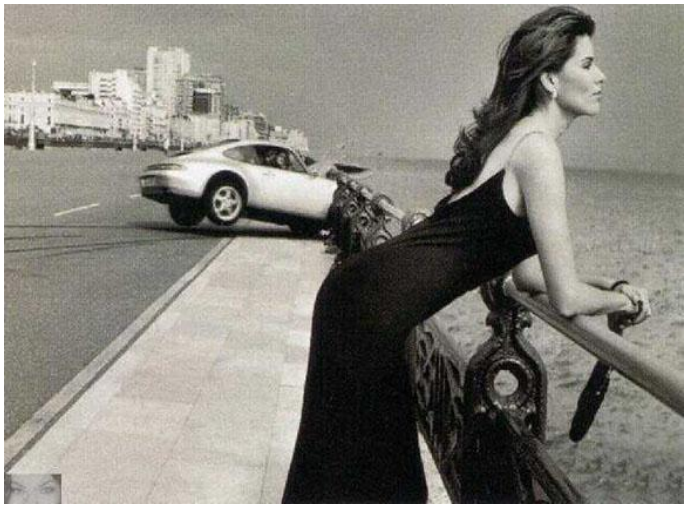
Stratified Medicine
Focusing on the right target?



Overview:

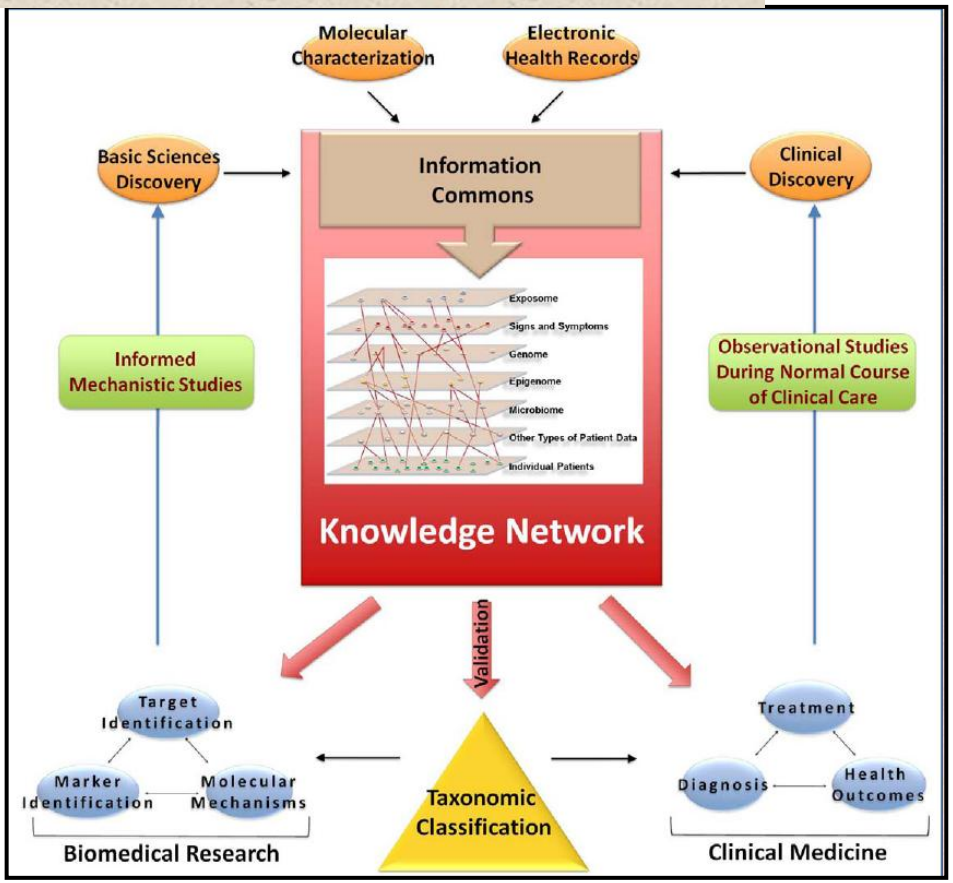
Are we measuring what counts ?

How do we reckon it will make a difference ?

Are there research designs that might inform us better ?

TOWARD PRECISION MEDICINE

Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease



Committee on A Framework for Developing a New Taxonomy of Disease

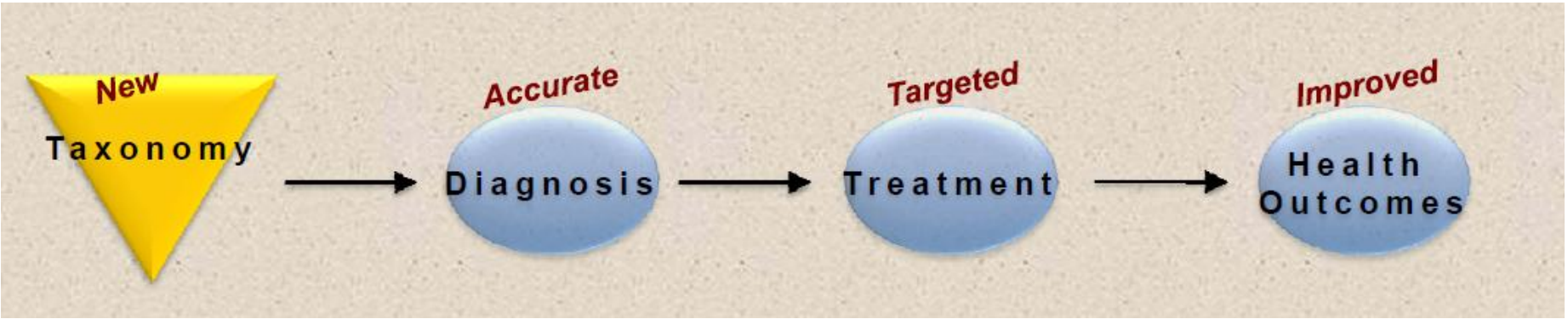
NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

TOWARD PRECISION MEDICINE

Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

Committee on A Framework for Developing a New Taxonomy of Disease

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES



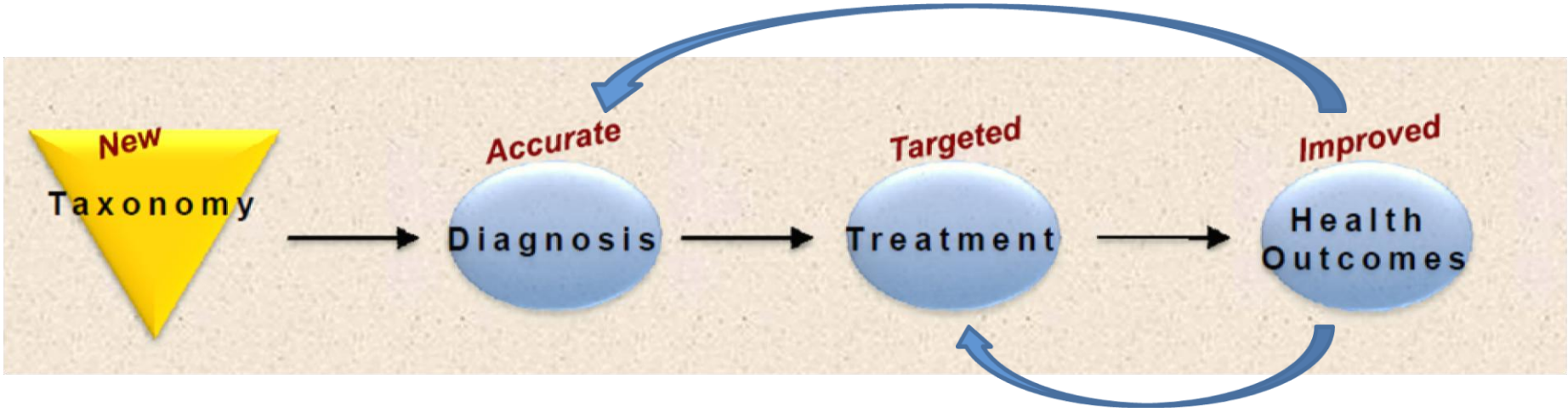
Patient 1: Consulting with her medical oncologist following breast cancer surgery.

Precise diagnosis based on specific molecular characteristics of patient and her cancer

Physician has multiple therapeutic options available

Therapeutic regimen tailored to focus on her particular tumor markers

Patient's relatives can undergo testing to assess their individual breast cancer predisposition.



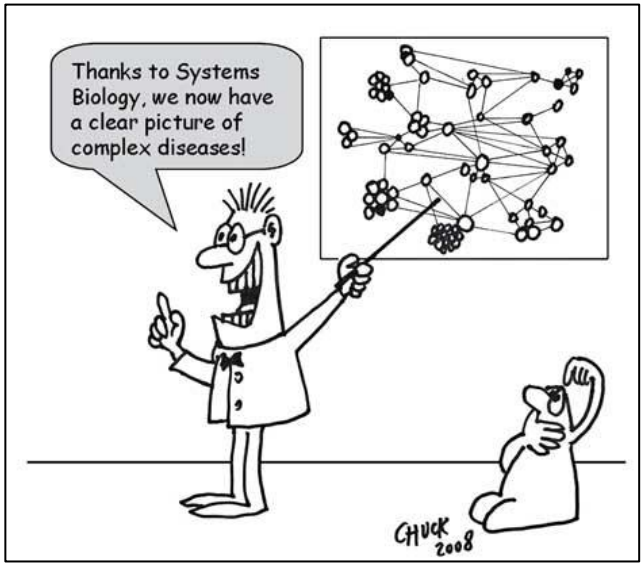
Precise diagnosis based on specific molecular characteristics of patient and her cancer

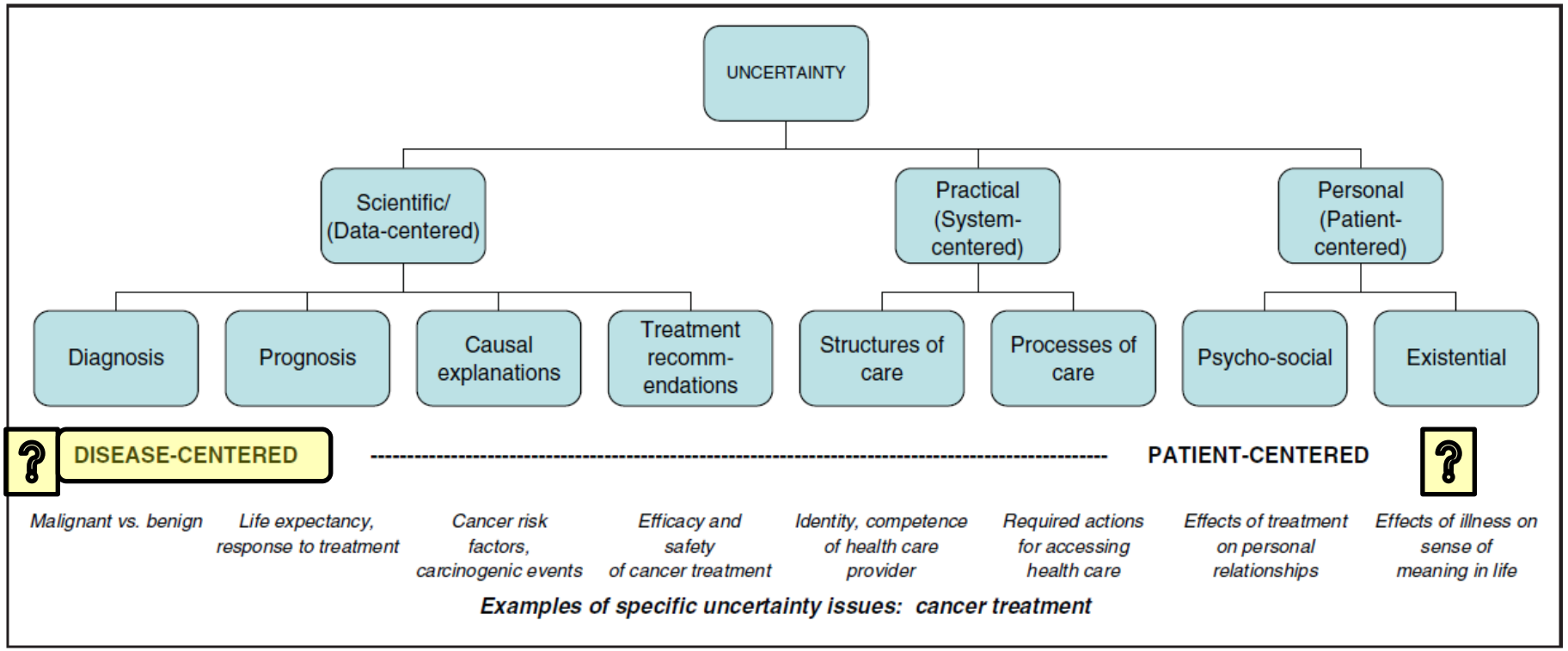
Therapeutic regimen tailored to focus on her particular tumor markers

CMAJ

EDITORIAL

Personalized medicine: a windfall for science, but what about patients?





Examples of specific uncertainty issues: cancer treatment

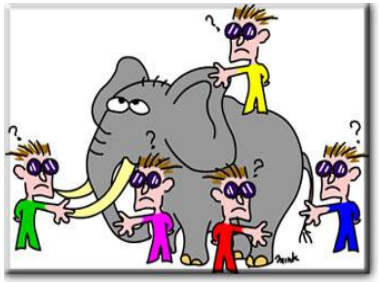
A taxonomy of judgements and decisions in *stratified medicine*

- Aetiological heterogeneity
  - *affecting (+/-) means / choice of diagnosis*
  - *affecting* (+/-) choice of treatment
- How magnitude of treatment benefit is affected by
  - baseline absolute risk of target outcome
  - distribution of subgroup "biomarker"

Measurement precision / responsiveness for outcome

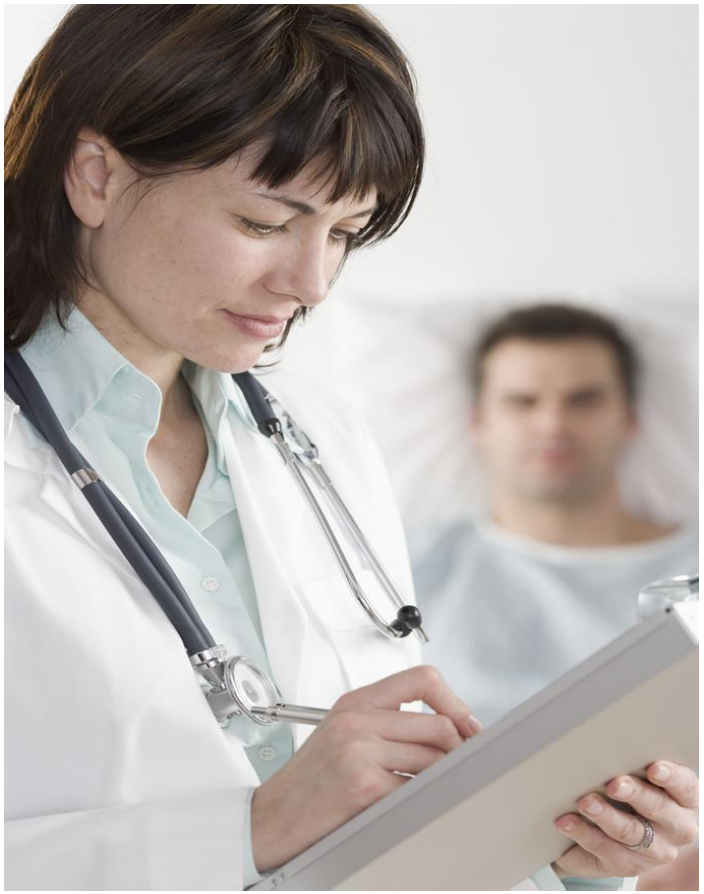
- Which outcomes valued by patient

  (Prevention versus treatment)
- Trade-off between NNT and NNH
  - How it might vary according to anticipated remaining life expectancy



What are the sorts of decisions that the doctor might make ?

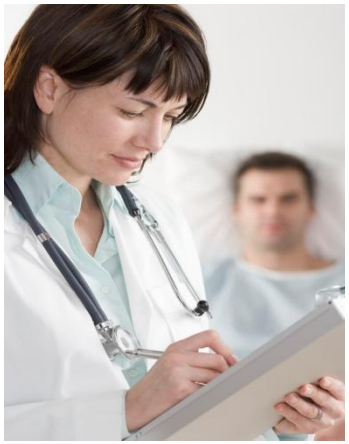
- Don’t treat;
  - watch and wait
- Treat with X instead of Y
- Tailor the dose of X



- You are conducting an RCT comparing the impact of two drugs, using the FICTION-L score (which is scaled to have a mean of 50 and SD of 10). There are 400 patients enrolled in each arm. You want to know whether there is a clinically important difference between arms at the end of the trial.

  How large a mean FICTION-L difference would make you quite confident that this had occurred ?

- A. 5 points
- B. About 6-7 points
- C. About 15-20 points



$\sqrt{\{2\sigma^2/N\}} = (10/20)\sqrt{2} \rightarrow$

95%CI = +/- 1.4 B

- You are an oncologist concerned that a new chemotherapeutic regimen is causing functioning loss in Patient X. To make an informed evaluation, you ask X to complete two FICTION-L assessments, one month apart.

  How large a FICTION-L change would make you quite confident that clinical important deterioration had occurred ?

- A. 5 points
- B. About 6-7 points
- C. About 15-20 points

$\sigma\sqrt{2}\{1- r_{xx}\} \rightarrow$ 95% CI {9-15.6} thus exceeding the 5 point margin with confidence requires 15-20 points change C

Table 1 Estimation and error for group comparisons and individual assessments with health status measure X

	Group comparison	Individual assessment	Individual change assessment
To estimate	The population difference $\mu_1 - \mu_2$, a property of populations that cannot be directly observed. It is the (theoretical) difference between two population means	The true score of person *i* on X, $E(X_i)$, an attribute of a person that cannot be directly observed. It is the expected value for person *i* on measure X, the (theoretical) average X would attain if person *i* were to produce many repeated independent values	The true change of person *i* on X, $E(X_{2i} - X_{1i})$, an attribute of a person that cannot be directly observed. It is the expected value of the change for person *i* on measure X, the (theoretical) average difference if person *i* were to produce many repeated independent values at Time 1 and Time 2
From sample	$\bar{X}_1 - \bar{X}_2$, the observed difference between the means of two samples	X_i, a single measurement of person *i*	$X_{2i} - X_{1i}$, a single measured change of person *i*
With error	The standard error of the difference in means[a], $\hat{\sigma}\sqrt{2/n}$	The standard error of measurement[b] for X, $\hat{\sigma}\sqrt{1 - r_{xx'}}$	The standard error of the measured difference[c] in X, $\hat{\sigma}\sqrt{2(1 - r_{xx'})}$
Theoretical precision	Unlimited, for large *n*	Limited by $r_{xx'}$	Limited by $r_{xx'}$

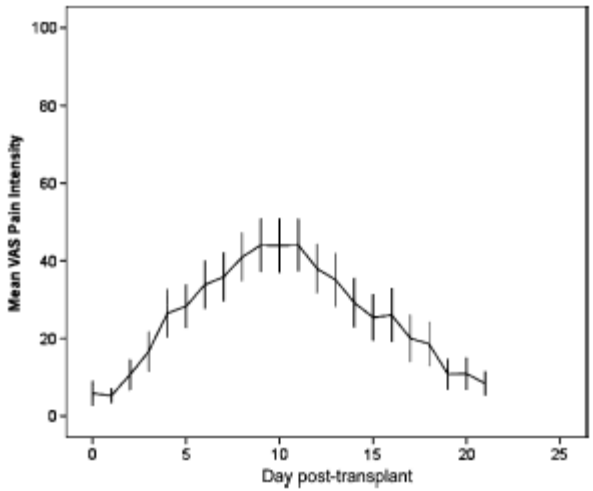


Fig. 1 Mean daily visual analog scale pain intensity scores (range 0–100) from 116 patients experiencing oral mucositis in the 3 weeks following bone marrow transplantation on Day 0. The plot shows the 95% confidence intervals for the mean scores on each day

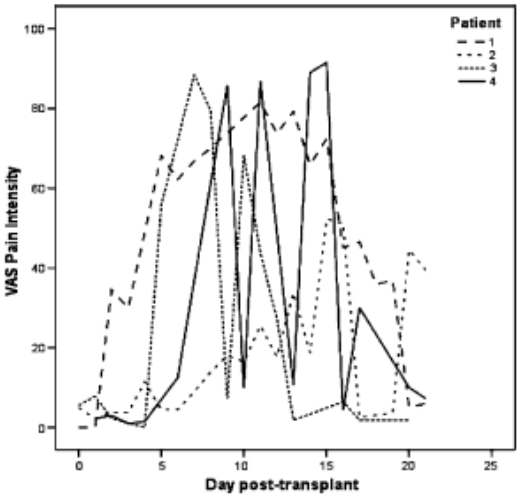
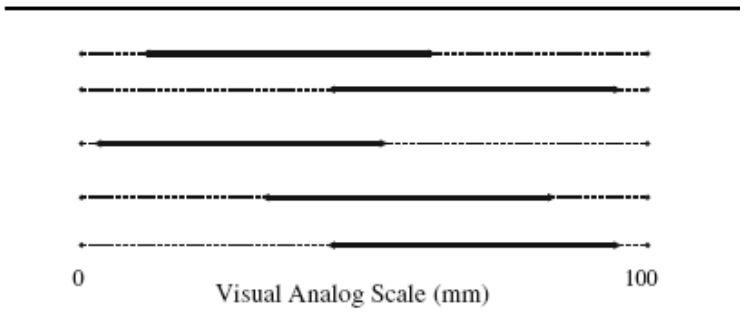


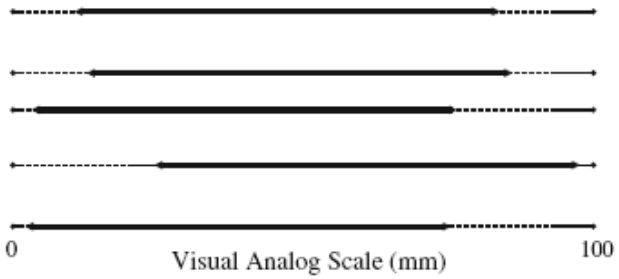
Fig. 2 Daily visual analog scale pain intensity scores (range 0–100) for four randomly selected patients who contributed data to Fig. 1. The plot shows the individual daily VAS pain reports in the 3 weeks following bone marrow transplantation at Day 0

Interpreting patient reported outcome results: US FDA guidance methods and emerging methods

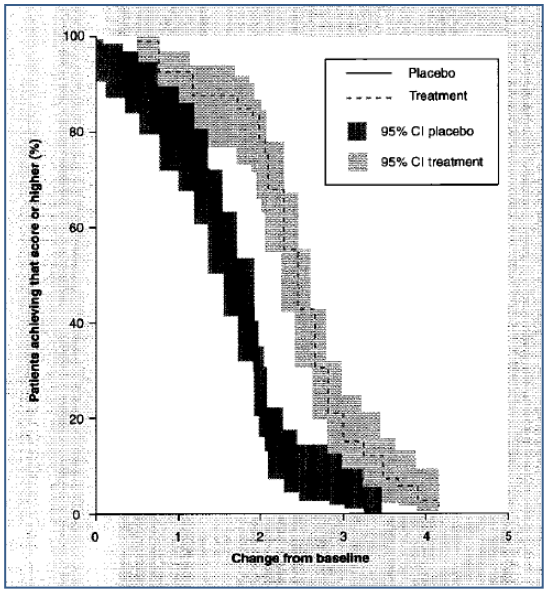
Expert Rev Pharmacoeconomics outcomes Res 2011; 11(2): 163-9



Hypothetical data depicting conventional confidence levels based on SEMs of 13%. The 95% confidence intervals extend about 26% in both directions, spanning 52% of the range of the scale



Hypothetical data depicting conventional confidence levels for measured change. When the SEM for a single assessment is 13%, the SEM for the measured change is 18% ($\sqrt{2}$ times 13%), and 95% confidence intervals extend about 36% in both directions. Confident assessment of change (by the conventional standard) therefore spans about 72% of the VAS scale



"Group change and individual change have different standard errors and thus group level estimates should not be used to define responders. A minimum criterion for a responder should be that the individual improved significantly ie that individual change is greater than the measurement error associated with the PRO measure "

"The average change on a measure for a group that was classified as improved, on an external anchor, does not necessarily equate to change that is sufficiently large to yield confidence that individual change has occurred"

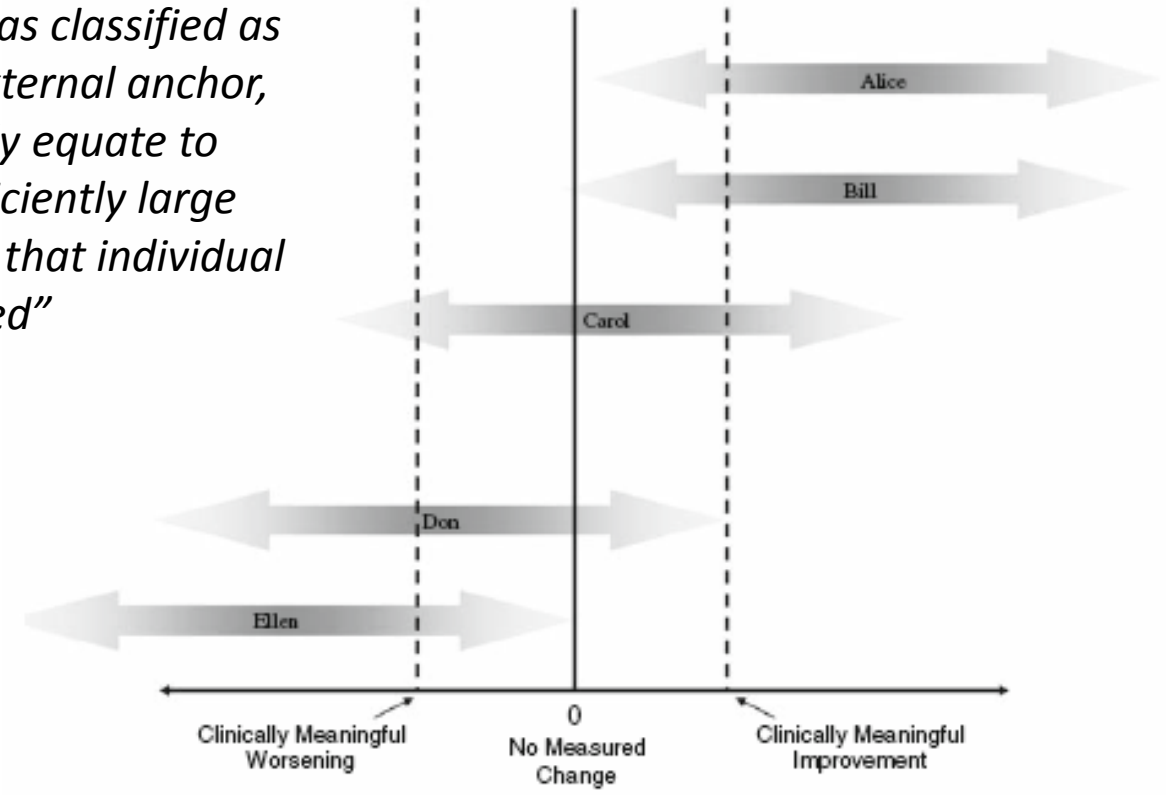


Fig. 8 A schematic interpretive context for confidence intervals. Conventional representations of confidence intervals graphically connote uniformity within the interval. This can be misleading when the interval bounds an estimate of an individual's value, such as health status or a change in health status. Interpretation of individual estimates should focus on the "likely values" rather than the unlikely values, even though both are subsumed under confidence intervals of conventional width. The likely values for *Alice* and *Bill* exceed the criterion for meaningful improvement, while the likely values for *Ellen* are below the criterion for meaningful worsening. *Don's* likely values showed statistical, but not clinically meaningful, worsening. *Carol's* likely values were consistent over time

Priorities and standards in pharmacogenetic research

Need, Motulsky, Goldstein. Nature Genetics 2005

In pharmacogenetics, the first step is usually the hardest: careful thought must go into choosing the most appropriate way to define response, and this should precede genetic analysis.

It seems too rarely appreciated that the appropriate definition of response (in terms of safety and efficacy) is often not obvious….It can be surprisingly difficult to represent even "simple" phenotypes like dose-response

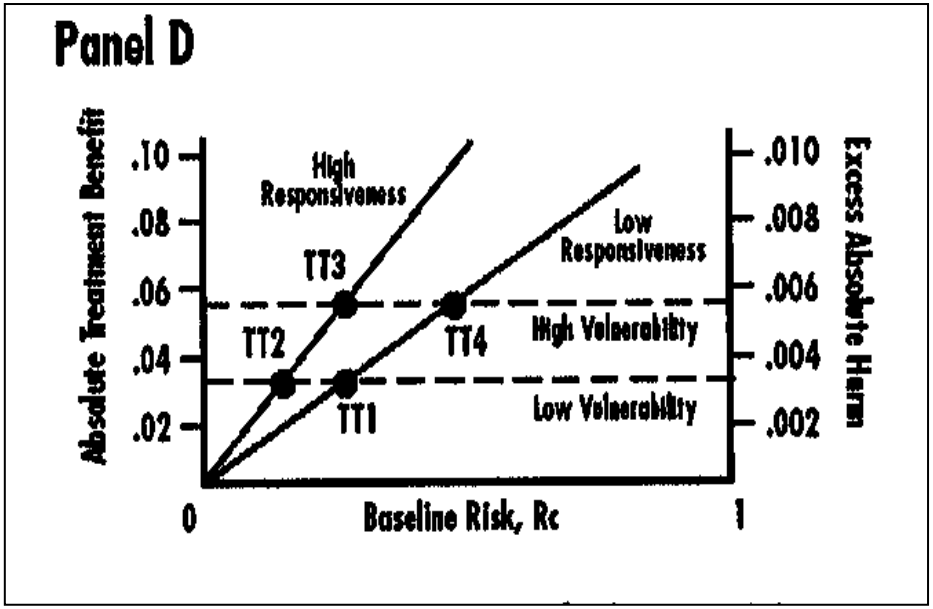
PHENOTYPE FIRST

What you need to know:

- Outcomes with and without knowledge of genotype
- How does P-G strategy alter the outcomes ?
- Therapeutic range of drug involved
- Alternative therapeutic options available
- How effective are monitoring strategies for ADR and prediction of response ?

NACB, 2006

What is of concern to the patient?



- What are the odds of benefit versus the odds of harm ?
  - (NNT and NNH useful).
- What is the added benefit of treatment that justifies the risks and toxicities of treatment?

"If pharmaco-genetics is to be a success, we need to get away from the perception that genetic data is special"

- **"My very own medicine: what must I know"**

Melzer D. 2003. Univ Cambridge/Wellcome

But each of these has multiple layers and accompanying issues

- Valuation of health states and QoL
- Patients trade-offs between side-effects of P_X and additional survival
- Patient's rate of time discounting
- Patient's own engagement with decision making and adherence to treatment

Value of Information on Preference Heterogeneity and Individualized Care

Anirban Basu, PhD, David Meltzer, MD, PhD

Med Decis Making 2007;27:112–127

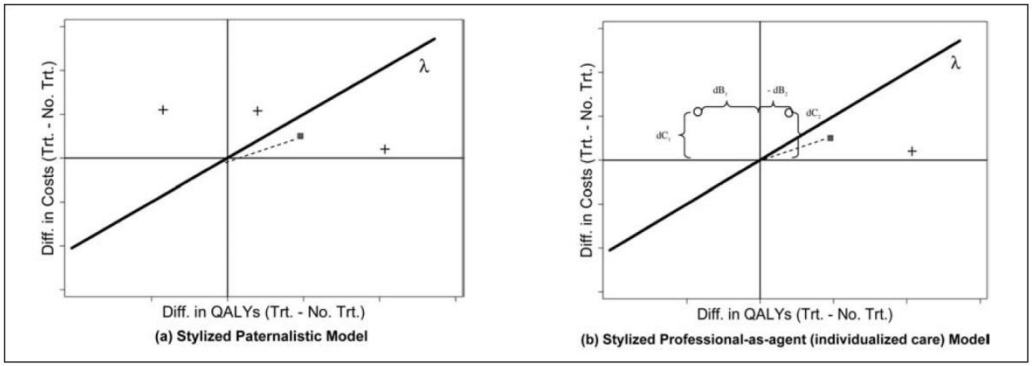


Figure 1 Illustration of the concept of expected value of individualized care (EVIC). λ = threshold cost-effectiveness ratio; o = physician's choice is no treatment; + = physician's choice is treatment. ■ = mean incremental costs and benefits. QALY, quality-adjusted life year.

"Therefore, the additional value of achieving individualized care .....is about 100 times the value of identifying cost-effective treatment on average, an exercise that the research literature on cost effectiveness analysis has primarily focused on over the past decade...."

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Preparing for Precision Medicine

Reza Mirnezami, M.R.C.S., Jeremy Nicholson, Ph.D., and Ara Darzi, M.D.

Ms. H. is a 35-year-old woman from Japan who has had a cough for 3 weeks. Her physician sends her for an x-ray and CT scan that reveal an advanced lesion, which a biopsy confirms to be non–small-cell lung cancer. She has never smoked. Can anything be done for her?

Had Ms. H.'s cancer been diagnosed before 2004, her oncologist might have offered her a treatment to which about 10% of patients have a response, with the remainder gaining a negligible survival benefit and experiencing clinically significant side effects. But her diagnosis was made in 2011, when her biopsy tissue could be analyzed for a panel of genetic variants that can reliably predict whether the disease will respond to treatment. Her tumor was shown to be responsive to a specific targeted agent, whose administration led to a remission lasting almost a year; her only side effect was a rash.

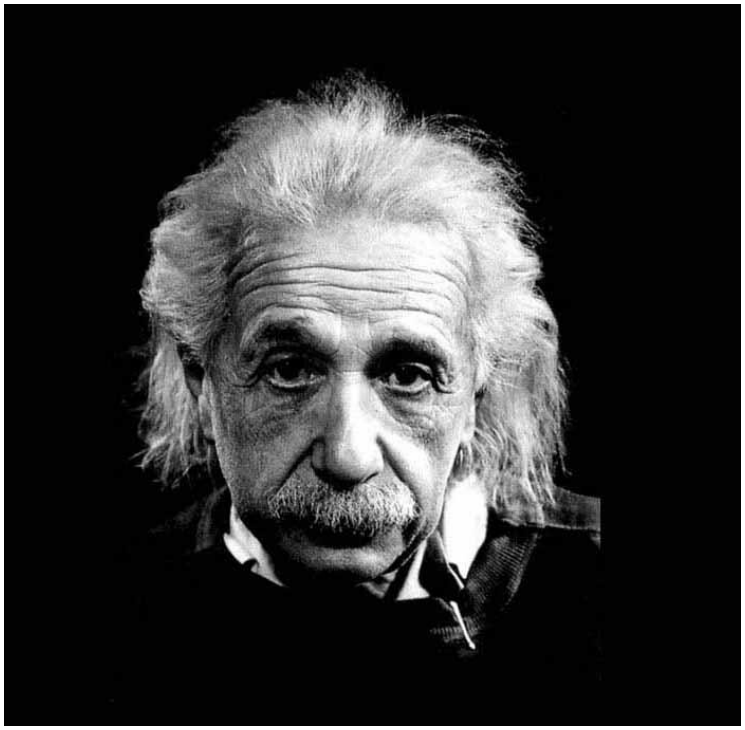
This scenario illustrates the fundamental idea behind personalized medicine: coupling established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements — hence the term "precision medicine." Recent biotechnological advances have led to an explosion of disease-relevant molecular information, with the potential for greatly advancing patient care. However, progress brings new challenges, and the success of precision medicine will depend on establishing frameworks for regulating, compiling, and interpreting the influx of information that can keep pace with rapid scientific developments. In addition, we must make health care stakeholders aware that precision medicine is no longer just a blip on the horizon — and ensure that it lives up to its promise.

First, consider regulation: precision medicine is expected to herald a rapid acceleration in the identification and development of next-generation pharmacotherapies. Currently, medical research organizations are calling for regulatory bodies to review the regulation of clinical trials, citing excessively lengthy approval processes as an impediment to the effective translation of basic science discoveries. According to Cancer Research U.K., there was a 65% increase in the time taken to gain approval for studies and a 75% increase in administrative costs between 2003 and 2007.[1] Moreover, there's no evidence to suggest that additional bureaucratic stringency has led to improved patient safety. It will be

The New England Journal of Medicine
Downloaded from nejm.org at QUEENS UNIV MED LIB on January 19, 2012. For personal use only. No other uses without permission.
From the NEJM Archive. Copyright © 2010 Massachusetts Medical Society. All rights reserved.

"Decision support tools have the potential to address these limitations and enable precision-medicine approaches to health care by providing clinicians and patients with individualized information and preferences, intelligently filtered at the point of care. They will provide clinicians with options for test ordering; indicate the sensitivity, specificity, and positive predictive value of tests; and aid clinical workflow by providing algorithms to facilitate decisions on the basis of test results"

“If I had an hour to solve a problem and my life depended on the solution, I would spend the first 55 minutes determining the proper question to ask, for once I know the proper question, I could solve the problem in less than five minutes.”



EDITORIAL | Annals of Internal Medicine

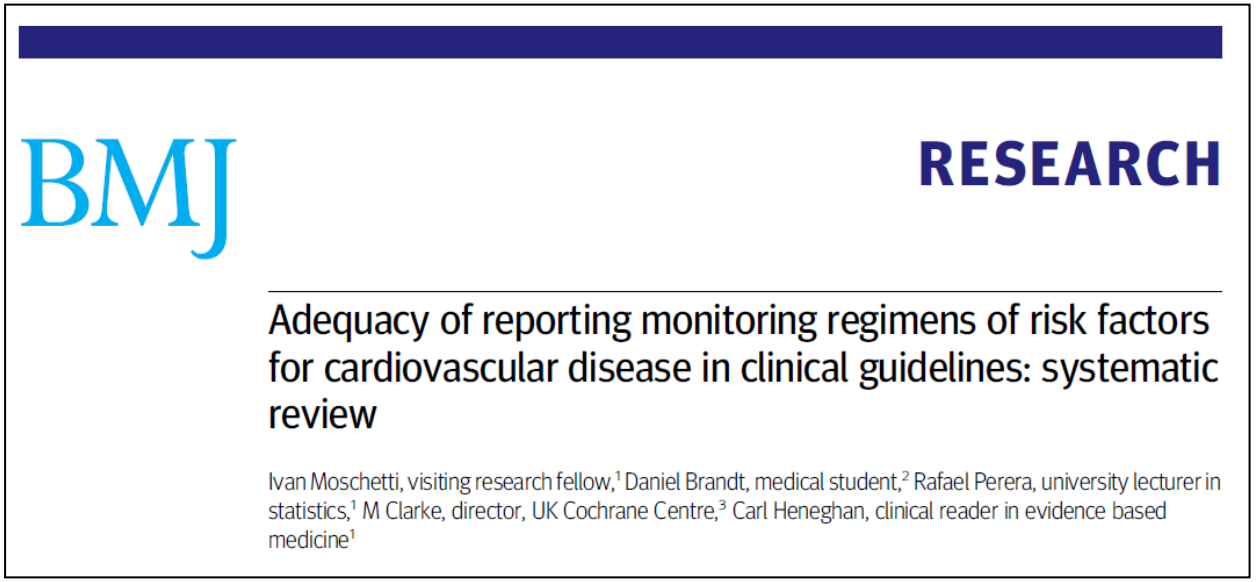
Terminal Ballistics of Kinase Inhibitors: There Are No Magic Bullets

Terminal ballistics is the study of the motion and consequent effects of projectiles, especially bullets, as they interact with their intended targets. How ammunition behaves once it enters and (sometimes) exits the body is crucial information for emergency physicians and trauma surgeons for optimal management of gunshot wounds (1). Since the "founder of chemotherapy," Paul Ehrlich, described a drug that would eliminate disease precisely and efficiently as a "magic bullet," oncologists have been prone to militaristic metaphors (2). For optimal care of patients with cancer, it has become increasingly important for oncologists and their internal medicine colleagues to study the terminal ballistics of the newest class of anticancer agents, kinase inhibitors.

ily reported by others (9), was a result of collaboration between oncologists and endocrinologists. As an extension of these observations, Desai and colleagues show that 36% of treated patients developed primary hypothyroidism and 62% had some abnormality of serum thyroid-stimulating hormone measurements. This careful work suggests that primary hypothyroidism is the basis for sunitinib-induced fatigue. Although the specific molecular mechanism is unclear, this toxicity might be due to damage to normal thyroid endothelium by sunitinib. In animal models, the capillary beds of glandular organs are particularly susceptible to VEGF inhibition, resulting in capillary regression (10). Thus, this might be a mechanism-related toxicity of sunitinib (and probably other potent VEGF receptor-2 in-

……we might serve our patients better by studying the terminal ballistics of new agents rather than persisting in our search for "magic bullets"

Ann Intern Medicine 2006



BMJ

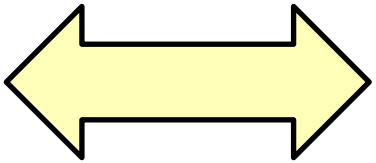
RESEARCH

Adequacy of reporting monitoring regimens of risk factors for cardiovascular disease in clinical guidelines: systematic review

Ivan Moschetti, visiting research fellow,[1] Daniel Brandt, medical student,[2] Rafael Perera, university lecturer in statistics,[1] M Clarke, director, UK Cochrane Centre,[3] Carl Heneghan, clinical reader in evidence based medicine[1]

Two truths

For groups,
on average



For individuals

Stratified Medicine
Focusing on the right target?

Patient-Reported Outcome Measures

FDA, CBER, CDER, CBRH