How Can We Assess Clinical Validity and Utility of Genome Profiles in Risk Assessment and Control of Cardiovascular Disease?

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Prediction is very difficult, especially about the future.

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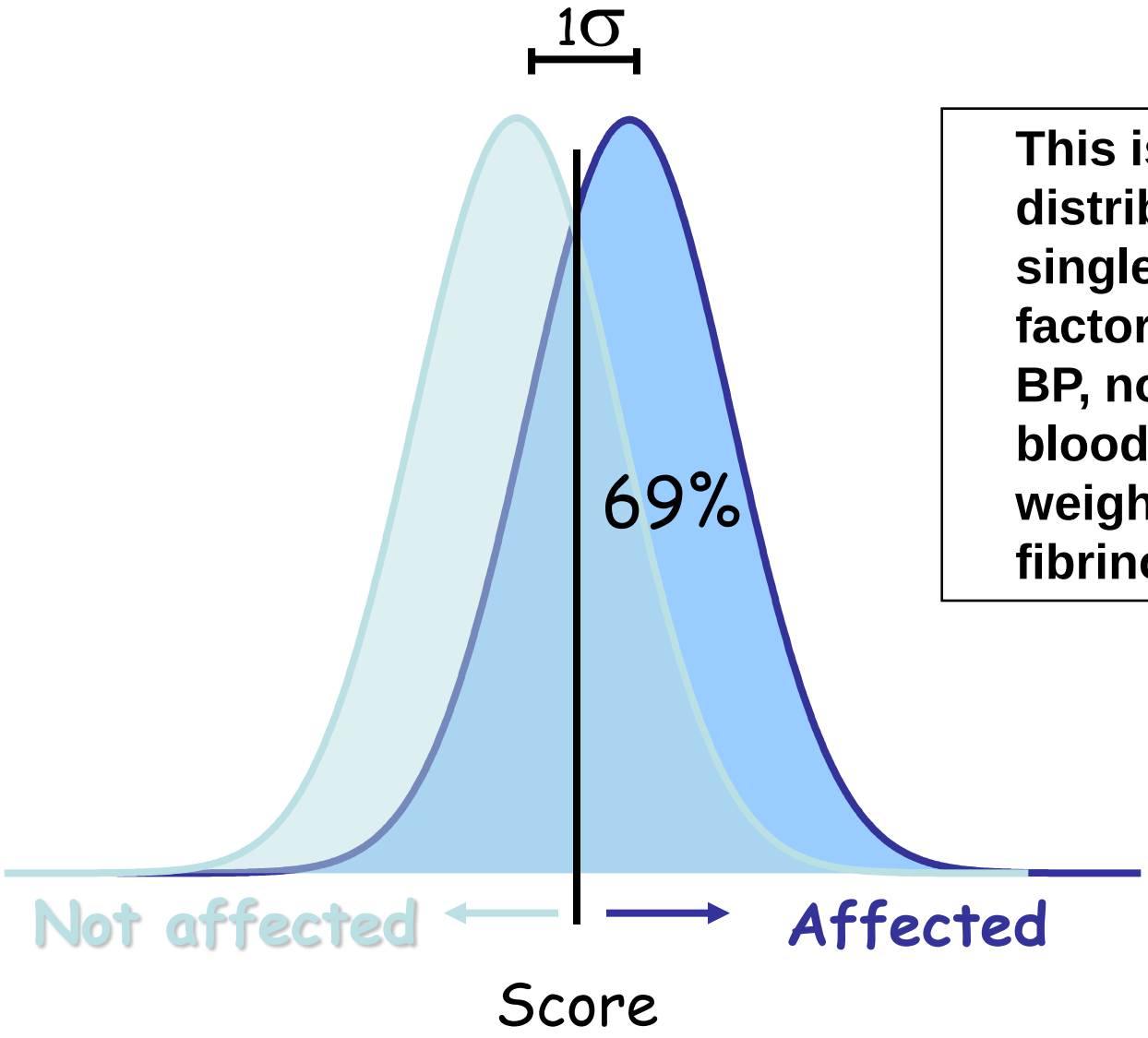
Niels Bohr

Danish physicist (1885 - 1962)

How do we define clinical validity and utility for *risk assessment?*

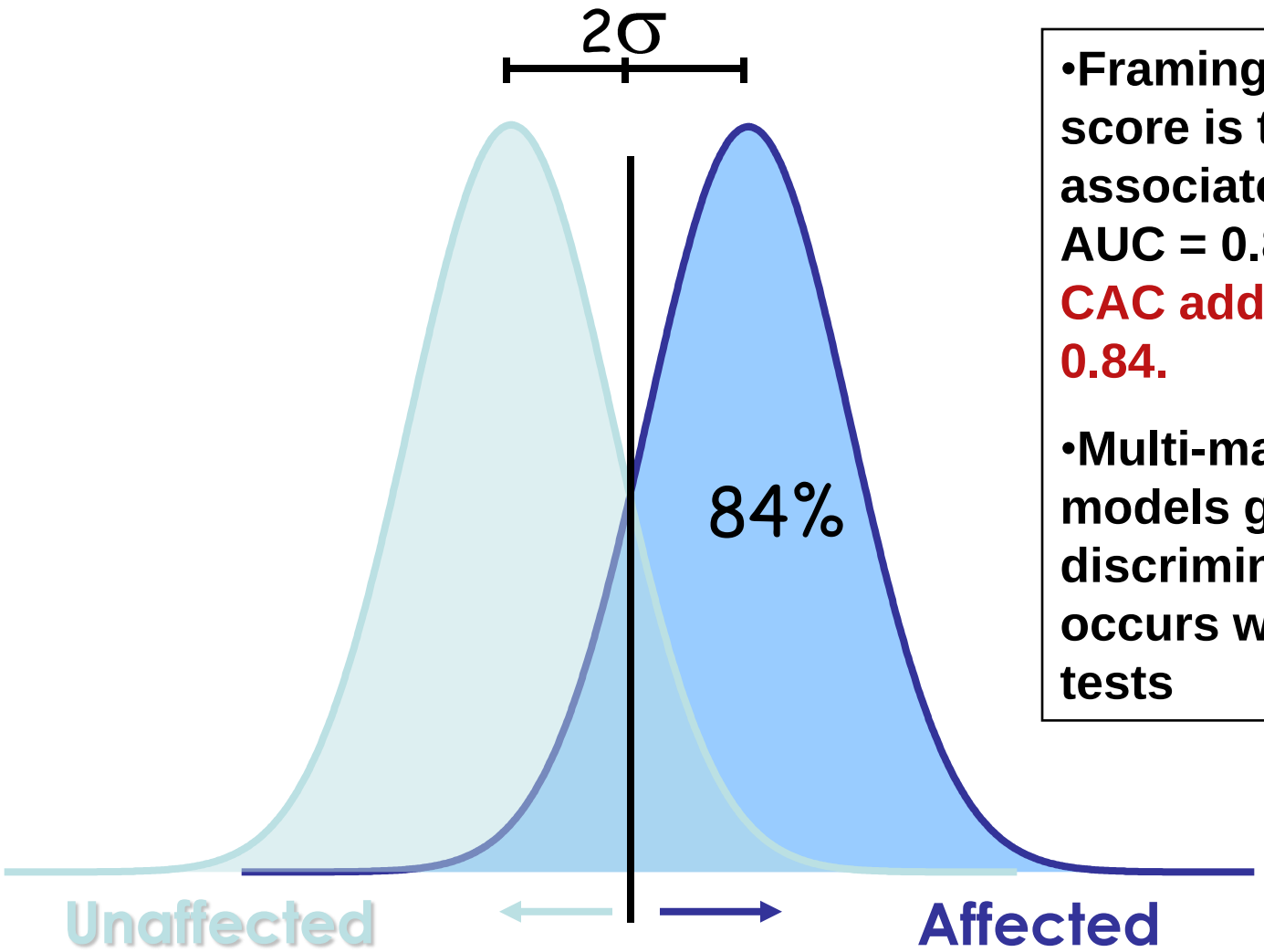
I. Step One: Assessments of the predictive capability of the test itself (Biomarker discovery and biomarker validation):
   - Additive predictive capability (independence in statistical models)
   - Discrimination – ability of the assessment method to distinguish affected from unaffected.
   - Calibration – predicted risk versus actual risk
   - Replication in different settings and different populations
   - Classification and reclassification – crossing agreed-upon and clinically meaningful treatment thresholds

Discriminating those who will get disease from those who won't?



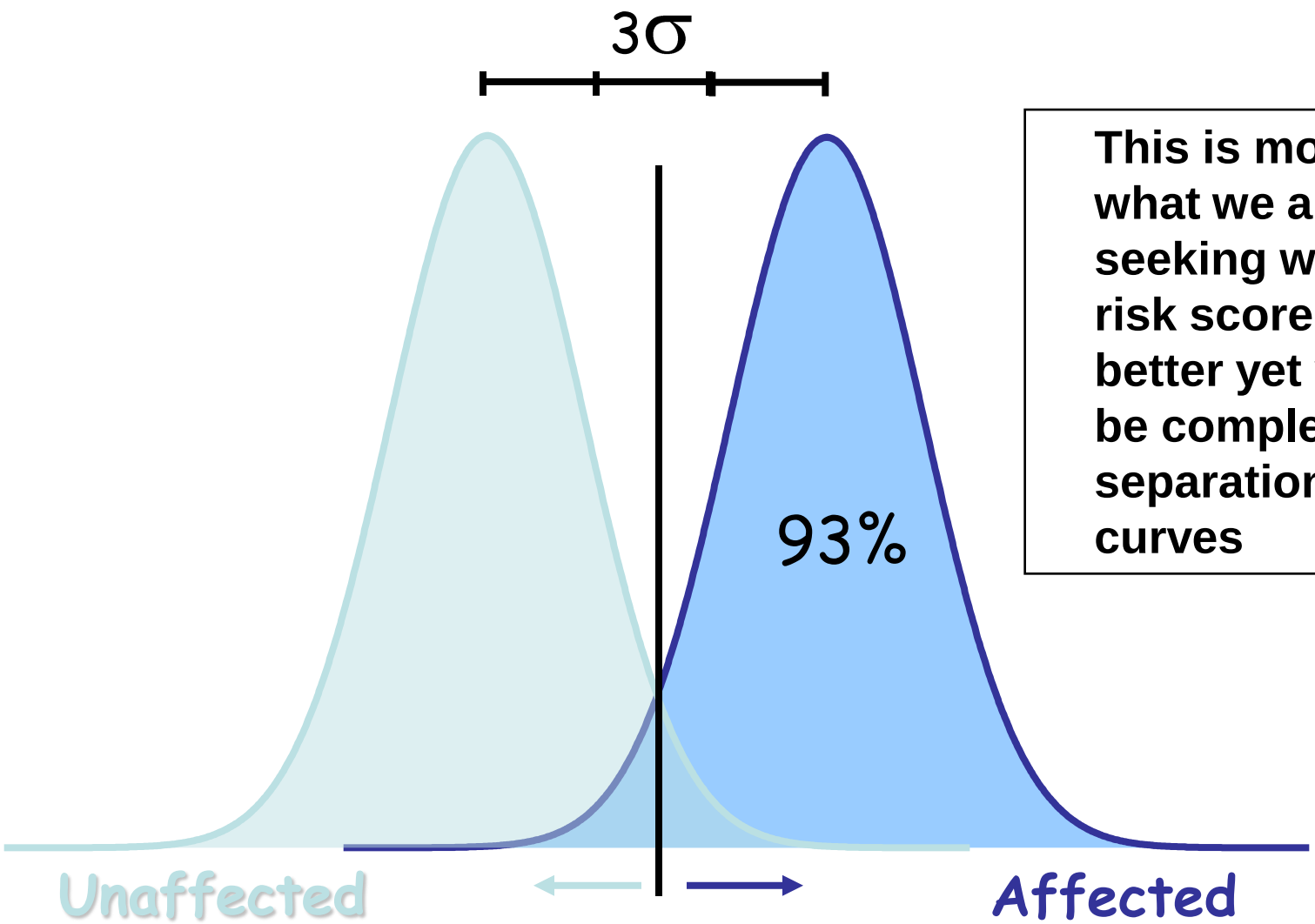
This is a typical distribution for single CVD risk factors: cholesterol, BP, no. of cigarettes, blood sugar, body weight; CRP; fibrinogen; etc.

Discriminating those who will get disease from those who won't?



- **Framingham risk score is typically associated with AUC = 0.80. With CAC added, AUC = 0.84.**
- **Multi-marker models give better discrimination than occurs with single tests**

Discriminating those who will get disease from those who won't?



This is more like what we are seeking with new risk scores – better yet would be complete separation of the curves

How do we define clinical validity and utility for *risk assessment?*

II. Step Two: Assessments of the clinical utility of the test:

- Can physicians do just as well *in prediction of CVD events* without using risk assessment tools?
- Do physicians *use risk assessment tools?* Rarely.
- Do risk assessment tools *improve patient outcomes?*
- What *kind of research* is needed at this time?

***BMJ* 1995;310:975-978.**

Do doctors accurately assess coronary risk in their patients? Results of the coronary health assessment study

Steven A Grover, Ilka Lowensteyn, Katja L Esrey, Yvonne Steinert, Lawrence Joseph, Michal Abrahamowicz

Do doctors accurately assess coronary risk in their patients?

- Doctors showed a strong understanding of the relative importance of specific risk factors, and most were confident in their ability to estimate coronary risk.
- While doctors accurately estimated the relative risk of a specific patient (compared with the average adult) they systematically overestimated the absolute baseline risk of developing coronary disease and the risk reductions associated with specific interventions.

Similar findings in other studies:

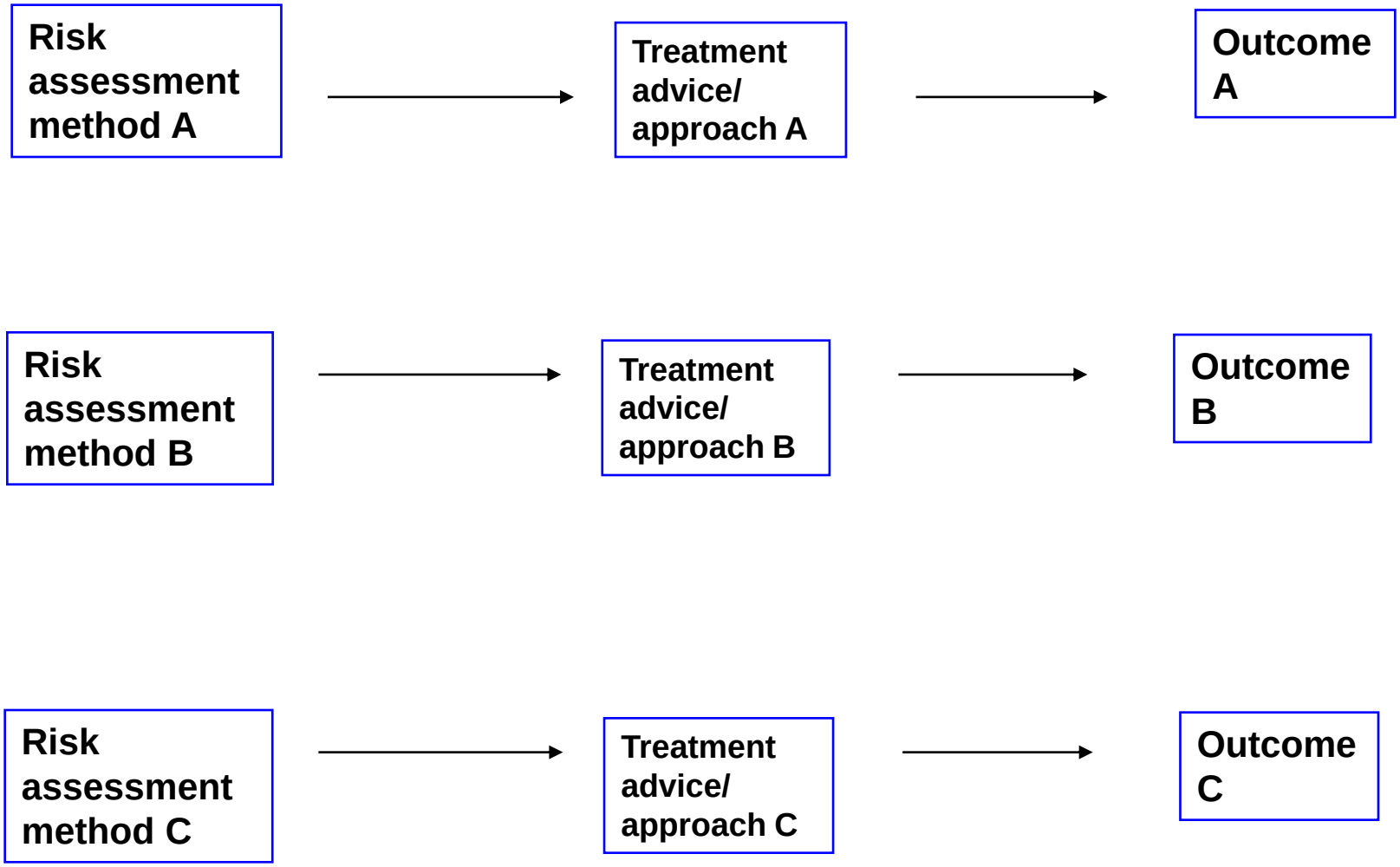
- Friedmann PD, Brett AS and Mayo-Smith MF: Differences in generalists‘ and cardiologists' perceptions of cardiovascular risk and the outcomes of preventive therapy in cardiovascular disease *Ann Intern Med* 1996, 124:414-21.

- Chatellier G, Blinowska A, Menard J and Degoulet P: Do physicians estimate reliably the cardiovascular risk of hypertensive patients? *Medinfo* 1995, 8 Pt 2:876-9.

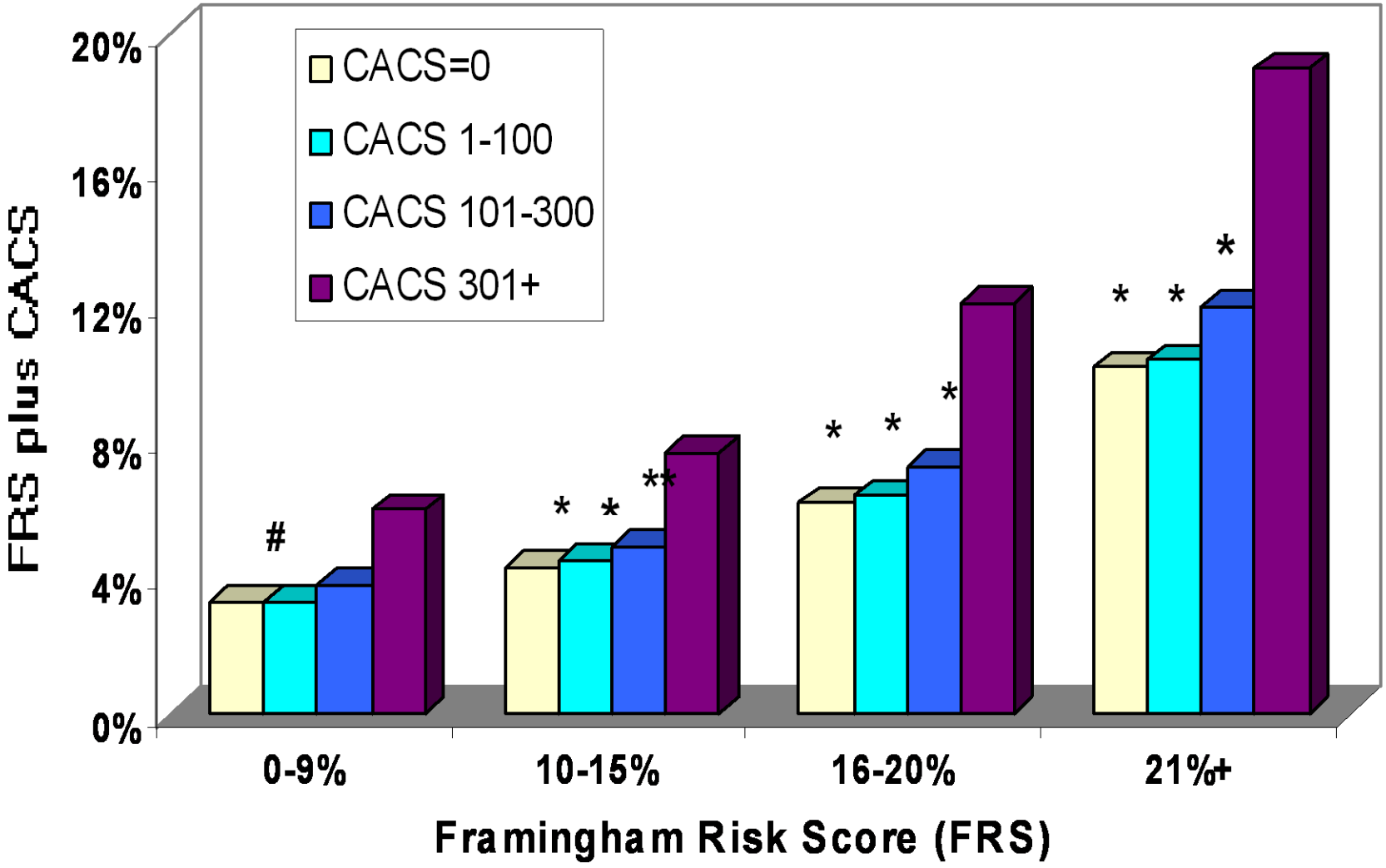
- McManus RJ, Mant J, Meulendijks CF, Salter RA, Pattison HM and Roalfe AK *et al.*: Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice: cross sectional study *BMJ* 2002, 324:459-64.

- Pignone M, Phillips CJ, Elasy TA, Fernandez A. Physicians' ability to predict the risk of coronary heart disease. BMC Health Serv Res. 2003 Jul 11;3(1):13.

What about Clinical Utility – Patient Outcome?



CT Calcium SCORES COMBINED WITH FRS FOR RISK PREDICTION



Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Robert Detrano, M.D., Ph.D., Alan D. Guerci, M.D., J. Jeffrey Carr, M.D., M.S.C.E., Diane E. Bild, M.D., M.P.H., Gregory Burke, M.D., Ph.D., Aaron R. Folsom, M.D., Kiang Liu, Ph.D., Steven Shea, M.D., Moyses Szklo, M.D., Dr.P.H., David A. Bluemke, M.D., Ph.D., Daniel H. O'Leary, M.D., Russell Tracy, Ph.D., Karol Watson, M.D., Ph.D., Nathan D. Wong, Ph.D., and Richard A. Kronmal, Ph.D.

NEJM, 2008

Detrano, et al, NEJM, 2008

Coronary Calcium as a Predictor of Coronary Events in Four Ethnic Groups

- HR's for major coronary events compared to CAC=0, with adjustment for major risk factors
  - 1-100: HR = 3.89
  - 101-300: HR = 7.08
  - >300: HR = 6.84
- AUC's for prediction of major events: For risk factors only, AUC = 0.79; RF's plus CAC: AUC = 0.83

The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review

N Waugh,[1*] C Black,[1] S Walker,[2] L McIntyre,[3] E Cummins[4] and G Hillis[5]

Executive summary

Health Technology Assessment 2006; Vol. 10: No. 39

For CT screening to be cost-effective, it has to add value over risk factor scoring, by producing sufficient extra information to change treatment and hence cardiac outcomes, at an affordable cost per quality-adjusted life-year. There was insufficient evidence to support this. Most of the NSC criteria were either not met or only partially met.

Impact of Electron Beam Tomography, With or Without Case Management, on Motivation, Behavioral Change, and Cardiovascular Risk Profile

A Randomized Controlled Trial

Patrick G. O'Malley, MD, MPH; Irwin M. Feuerstein, MD; Allen J. Taylor, MD

Conclusions Using coronary calcification screening to motivate patients to make evidence-based changes in risk factors was not associated with improvement in modifiable cardiovascular risk at 1 year. Case management was superior to usual care in the management of risk factors.

JAMA. 2003;289:2215-2223 www.jama.com

BMC Health Services Research

BioMed Central

Research article

Open Access

Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? A systematic review of the literature

Stacey L Sheridan*[1] and Eric Crespo[2]

BMC Health Services Research 2008; 8:60.

Abstract

Background: Guidelines now recommend routine assessment of global coronary heart disease (CHD) risk scores. We performed a systematic review to assess whether global CHD risk scores result in clinical benefits or harms.

Methods: We searched MEDLINE (1966 through June 13, 2007) for articles relevant to our review. Using predefined inclusion and exclusion criteria, we included studies of any design that provided physicians with global risk scores or allowed them to calculate scores themselves, and then measured clinical benefits and/or harms. Two reviewers reviewed potentially relevant studies for inclusion and resolved disagreement by consensus. Data from each article was then abstracted into an evidence table by one reviewer and the quality of evidence was assessed independently by two reviewers.

Conclusion: Our review provides preliminary evidence that physicians' knowledge of global CHD risk scores may translate into modestly increased prescribing of cardiovascular drugs and modest short-term reductions in CHD risk factors without clinical harm. Whether these results are replicable, and translate across other practice settings or into improved long-term CHD outcomes remains to be seen.

In other words, not a rousing endorsement of the clinical utility of risk assessment tools, based on clinical evidence as of 2008.

How good does the personalized risk assessment have to be?

Adherence	Trial Arm	Life-Years	Total Medical Costs	QALYs	ΔCost/ ΔQALY
100	Standard Care	119994	$5,328,763	66288	$80
100	Unconditional	140043	-$27,076,140	79000	cost saving
100	SHAPE wCACS	125357	$151,818,099	68807	$2,206
100	SHAPE wCIMT	121004	$108,718,583	65936	$1,649
100	Biomarkers	119095	$40,196,154	65101	$617

Costs and QALYs (in thousands). Effects of each of the trial arms at 100% adherence compared to a 0% adherence baseline. Results are for the full 35-year trial.

Prospect theory

Prospect theory was developed by Daniel Kahneman and Amos Tversky in 1979 (Nobel Prize work) as a psychologically realistic alternative to expected utility theory.

It allows one to describe how people make choices in situations where they have to decide between alternatives that involve risk, e.g. in financial decisions. Starting from empirical evidence, the theory describes how individuals evaluate potential losses and gains.

In the original formulation the term prospect referred to a lottery.

The Framing of Decisions and the Psychology of Choice

Amos Tversky and Daniel Kahneman

Science. 1981 Jan 30;211(4481):453-8

Journal of Risk and Uncertainty, 5:297–323 (1992)

Advances in Prospect Theory: Cumulative Representation of Uncertainty

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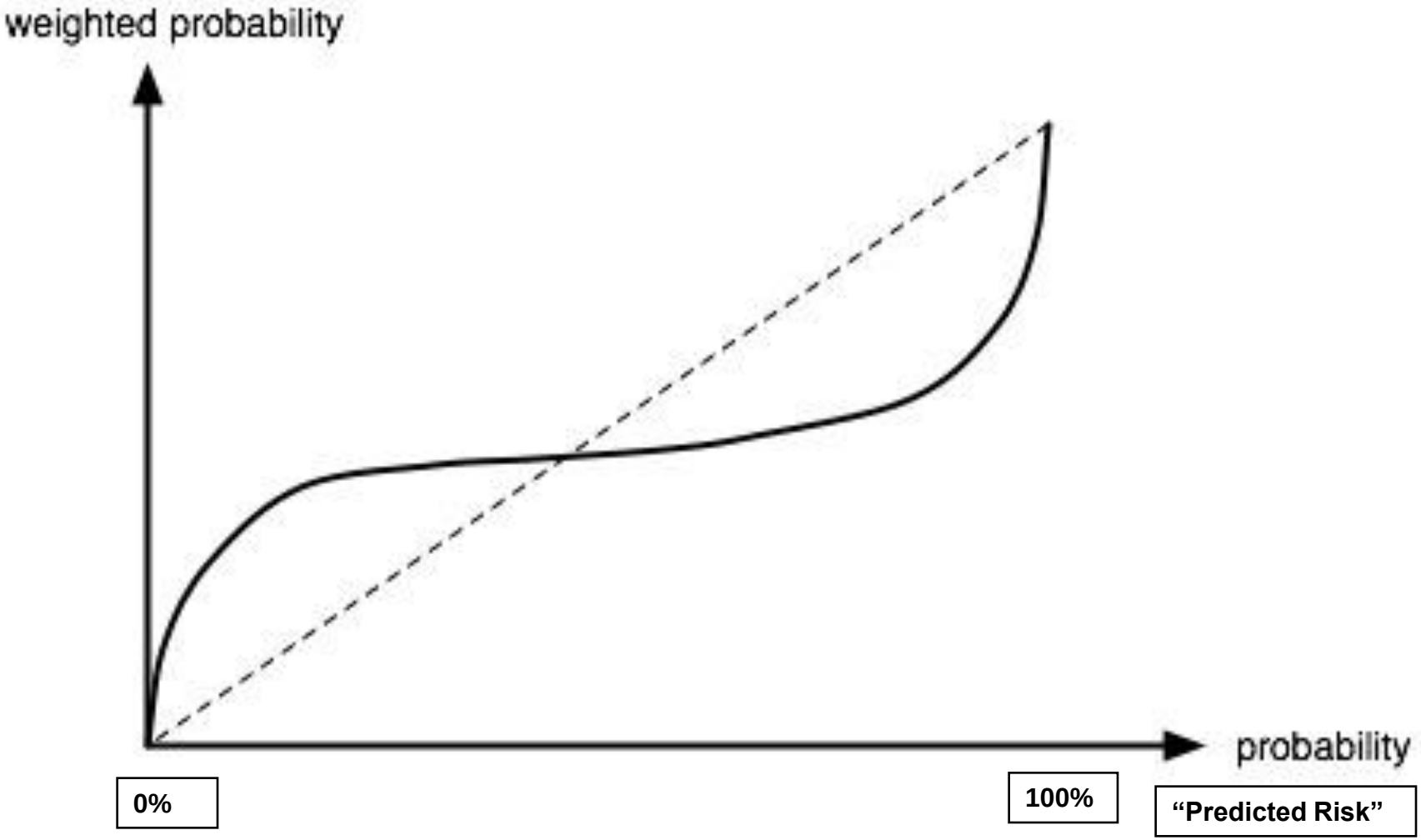
Key words: cumulative prospect theory

“People’s Behavior”



Conclusions

- Physicians *and patients* need better ways of making decisions about CVD risks – when to be tested, by what methods, and what to do about the results.
- Better tests are needed to assess risk. Current tests have *serious limitations,* and *routine treatment* without risk assessment may do better than test and treat.
- We need serious *breakthroughs in the predictive capability of new tests* – not necessarily in the way we evaluate new tests.
- We need better ways of *communicating risk*.
- We need to be convinced that *patient outcomes* can be improved following risk assessment.