Over innovatie, centen en patiënten: inzichten vanuit de industrie en de overheid

Frank Hulstaert
Promotie 1985

GENTSE SPRUITEN, 18 APRIL 2018

Sint-Gregoriuscollege in Ledeberg
6WA
1977-78

UGent
Geneeskunde
1978-85

VUB
Informatica
1987-92

UHasselt
Biostatistiek
1993-96

1978
1987

- Leerling assistent sportgeneeskunde, epidemiologie
- UCL medische statistiek, ASO interne UZGent

1987
1998

- Applied Artificial Intelligence nv
- IBM nv

1988
1992

- Becton Dickinson nv
  - Klinische exploratie flow cytometrie

1992
1997

- Sandoz-Novartis nv
  - Klinische ontwikkeling geneesmiddelen

1997
2004

- Innogenetics nv
  - Biomarkers en biotech

2004

- KCE
  - HTA en publicly funded trials

Meerdere groepen onderzoeken zelfde onderwerp
De publicatie competitie

Am Heart J. 1986 Sep;112(3):478-84.

Serum lipids and apoproteins in students whose parents suffered prematurely from a myocardial infarction.

De Backer G, Hulstaert F, De Munck K, Rosseneu M, Van Parijs L, Dramaix M.

Abstract

Lipids and apoproteins as well as other coronary risk factors were measured in offspring of patients who suffered from a myocardial infarction before the age of 50 years; the results are compared with the results of a control group matched for age and sex. Significant differences were observed in the apoprotein A1 level, in the protein/fat ratios of high- and low-density lipoproteins, and in smoking habits. In a multivariate analysis, the offspring group was found to be different from the control group in nonhigh-density lipoprotein cholesterol/apoprotein B ratio, high-density lipoprotein cholesterol/apoprotein A1 ratio, smoking habits, apoprotein A1, and apoprotein A2. By means of these variables a total of 85% of all subjects could be correctly classified. We conclude that as early as age 21 years the offspring of patients with premature coronary heart disease differ from matched control subjects in lipoprotein measurements and in smoking habits.

N Engl J Med. 1986 Sep 18;315(12):721-6.

The relation of apolipoproteins A-I and B in children to parental myocardial infarction.

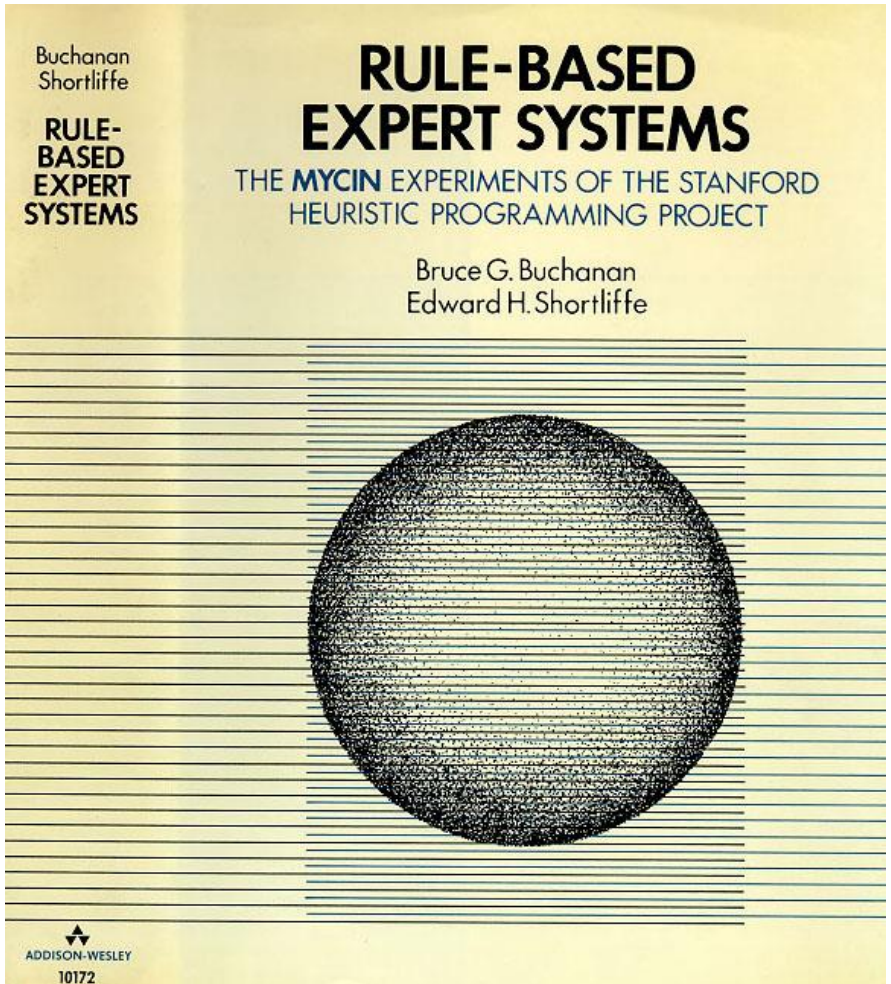
Freedman DS, Srinivasan SR, Shear CL, Franklin FA, Webber LS, Berenson GS.

Abstract

Clinical studies suggest that serum levels of apolipoproteins A-I and B may be more strongly related to coronary artery disease than are their respective lipoprotein-cholesterol fractions. Therefore, we assessed the association between levels of apolipoprotein B, apolipoprotein A-I, lipids, and lipoprotein cholesterols in children and the reported histories of myocardial infarction in their parents in a survey of 2416 black and white school-age children. As compared with children whose fathers did not report a myocardial infarction, those whose fathers reported having had an infarction (n = 139) had a lower mean level of apolipoprotein A-I (137 vs. 141 mg per deciliter; P = 0.04) and a lower ratio of low-density lipoprotein cholesterol to apolipoprotein B (1.08 vs. 1.11; P = 0.007), along with a higher ratio of apolipoprotein B to apolipoprotein A-I (0.64 vs. 0.61; P = 0.04). These associations existed independently of the children's race, sex, age, and history of obesity, smoking, alcohol intake, and use of oral contraceptives. Children whose mothers reported having had a myocardial infarction (n = 56) had no decrease in the ratio of low-density lipoprotein cholesterol to apolipoprotein B, but they tended to have an elevated ratio of apolipoprotein B to apolipoprotein A-I. In contrast, serum lipoprotein-cholesterol fractions in children were not related to myocardial infarctions in either parent. These results provide further evidence that apolipoproteins are more strongly related to the risk of cardiovascular disease than are lipoprotein-cholesterol fractions.

HULSTAERT, F., DE JONGHE, D., BOUCKAERT, A., DERWAEL, C. andBROCHET, C. (1987) The design of an expert system for the management of cardiac arrhythmias.*Computers in cardiology*, IEEE Computer Society, 231–234.

Google Scholar



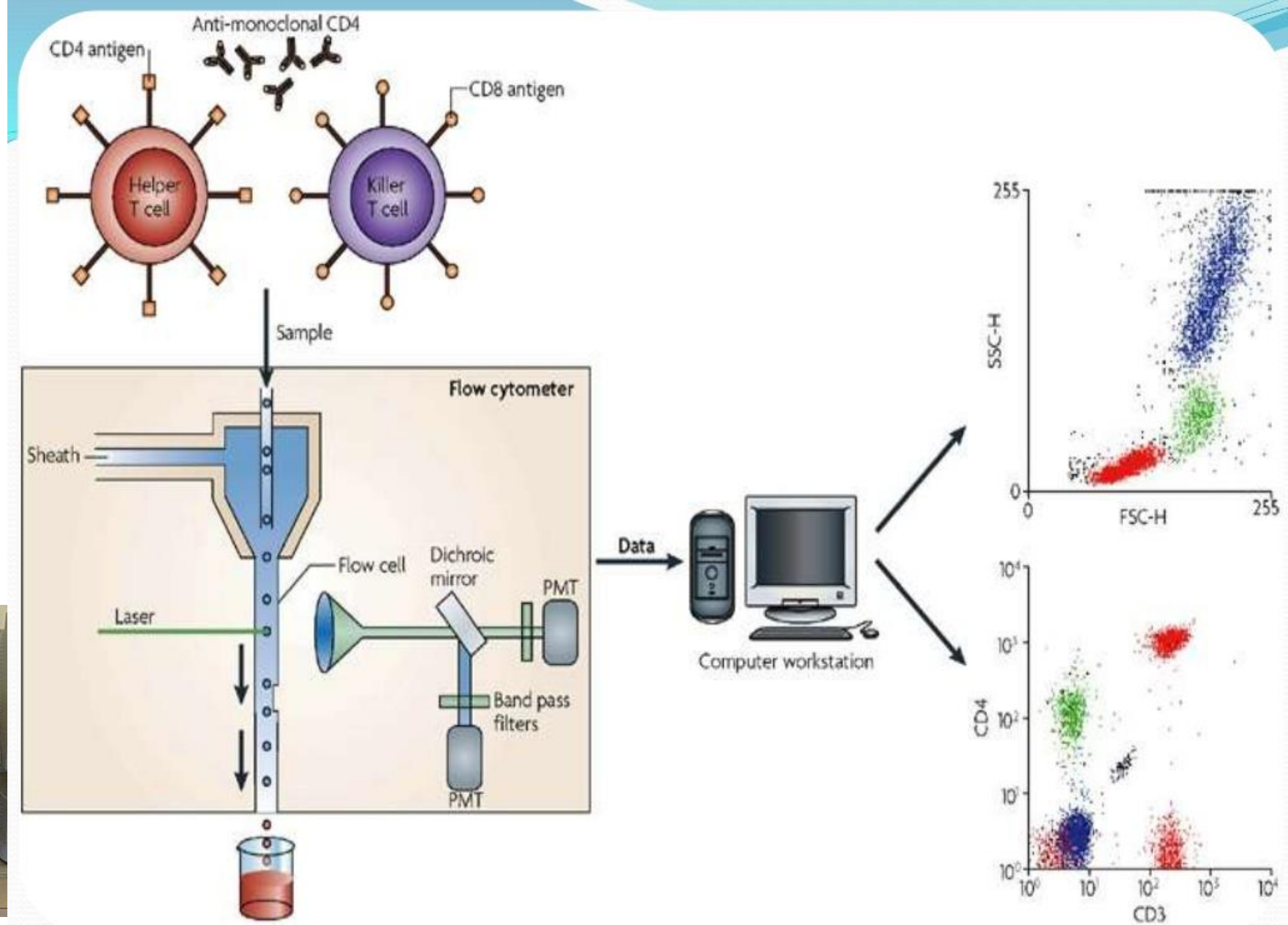
Lisp, Prolog
Rule-based expert system shells
Begin van neurale netwerken

30 jaar te vroeg

Flow cytometrie

De juiste technologie op de juiste tijd (1988)

CD4 T cel bepaling bij HIV (nog geen viral load)
+
Nieuwe onderzoeksmogelijkheden « for research use only »
=
Commercieel succes in de research markt



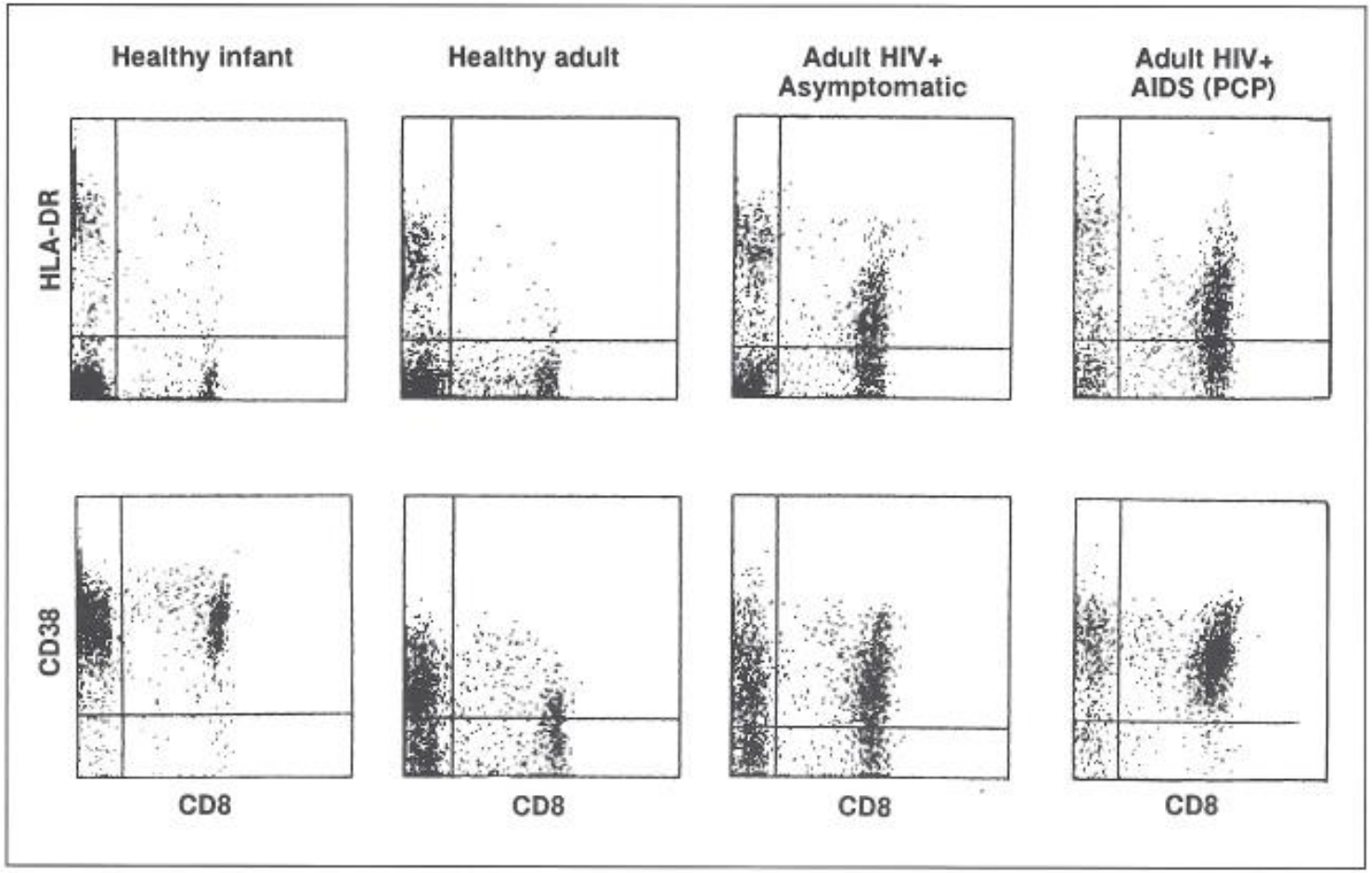


Fig. 1. Typical 2-color flow cytometry dotplots illustrating CD8 subsets defined using HLA-DR and CD38 expression in healthy infants and adults, as well as in asymptomatic and symptomatic HIV-1 seropositives.

The staging and prognostic value of subset markers on CD8 cells in HIV disease; in Janossy G, Autran B, Miedema F (eds) Immunodeficiency in HIV Infection and AIDS. EC/FERS/MRC Workshop on Immunodeficiency in HIV-1 infections, Windsor, Surrey, 1991, Basel, Karger, 1992, pp 185-194.

BECTON DICKINSON

Certificate of Training

This is to certify that

MR. F. HULSTAERT

has successfully completed

THE FACSCAN SERVICE TRAINING

Given at Becton Dickinson Belgium 30/04/1992

BY Dirk Damen Technical Support Manager Eu

Proefschrift Bijzonder Licentiaat Informatica, VUB, 1991-92.
Promotor: Prof Theo D'Hondt.
C++ objecten en methoden voor de analyse van flowcytometrie gegevens.

An optimized method for routine HLA-B27 screening using flow cytometry. Hulstaert F, Albrecht J, Hannet I, Lancaster P, Buchner L, Kunz J, Falkenrodt A, Tongio M, De Keyser F, Veys EM, et al. *Cytometry. 1994 Mar 15;18(1):21-9.*

BD Europe Helpdesk

+

Kennis FACScan(s)

+

Kennis Informatica

+

Validatie Studie

Een nieuwe HLA-B27 test *FDA approved*

Patent US6613535

Filed: 29 OCT 1992

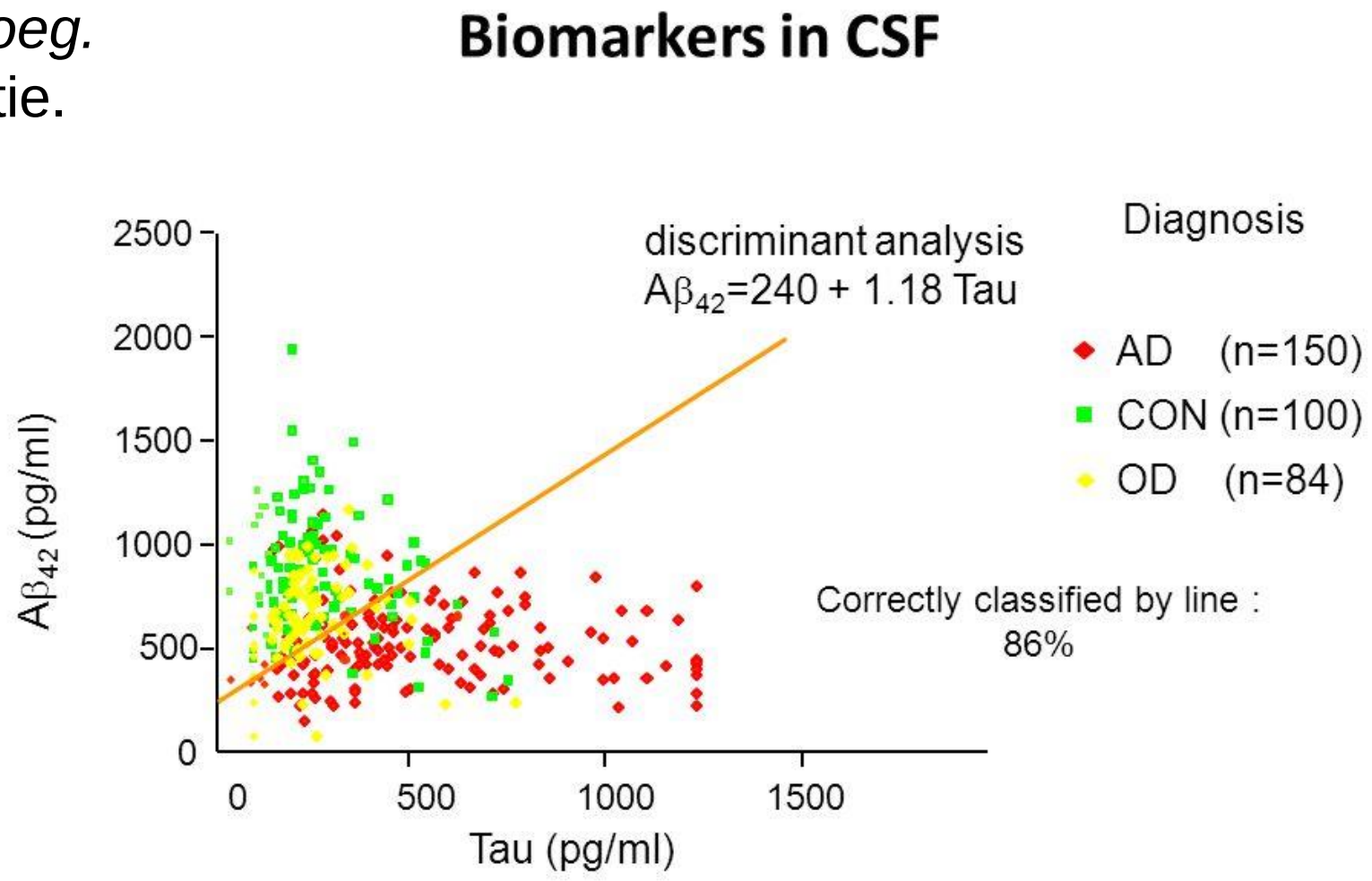
Publication: 2 SEP 2003

Assignee: Becton, Dickinson and Company

Inventors: Joachim Albrecht, Frank Hulstaert, Rosette Becker

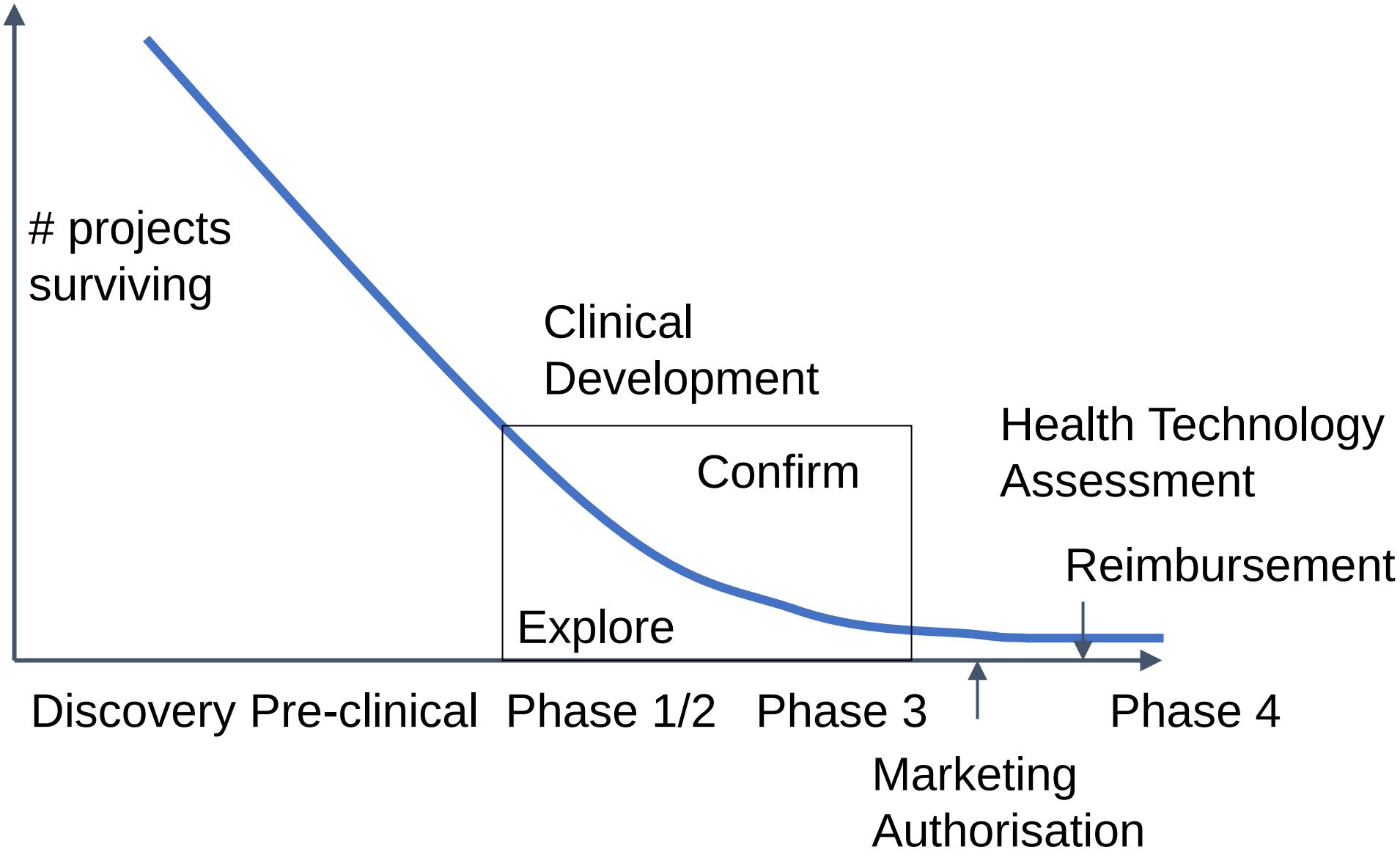
Vroegdiagnose van de ziekte van Alzheimer

Test kwam minstens 10 jaar te vroeg.
De kracht van een M&S organisatie.
Het oog wil ook wat.

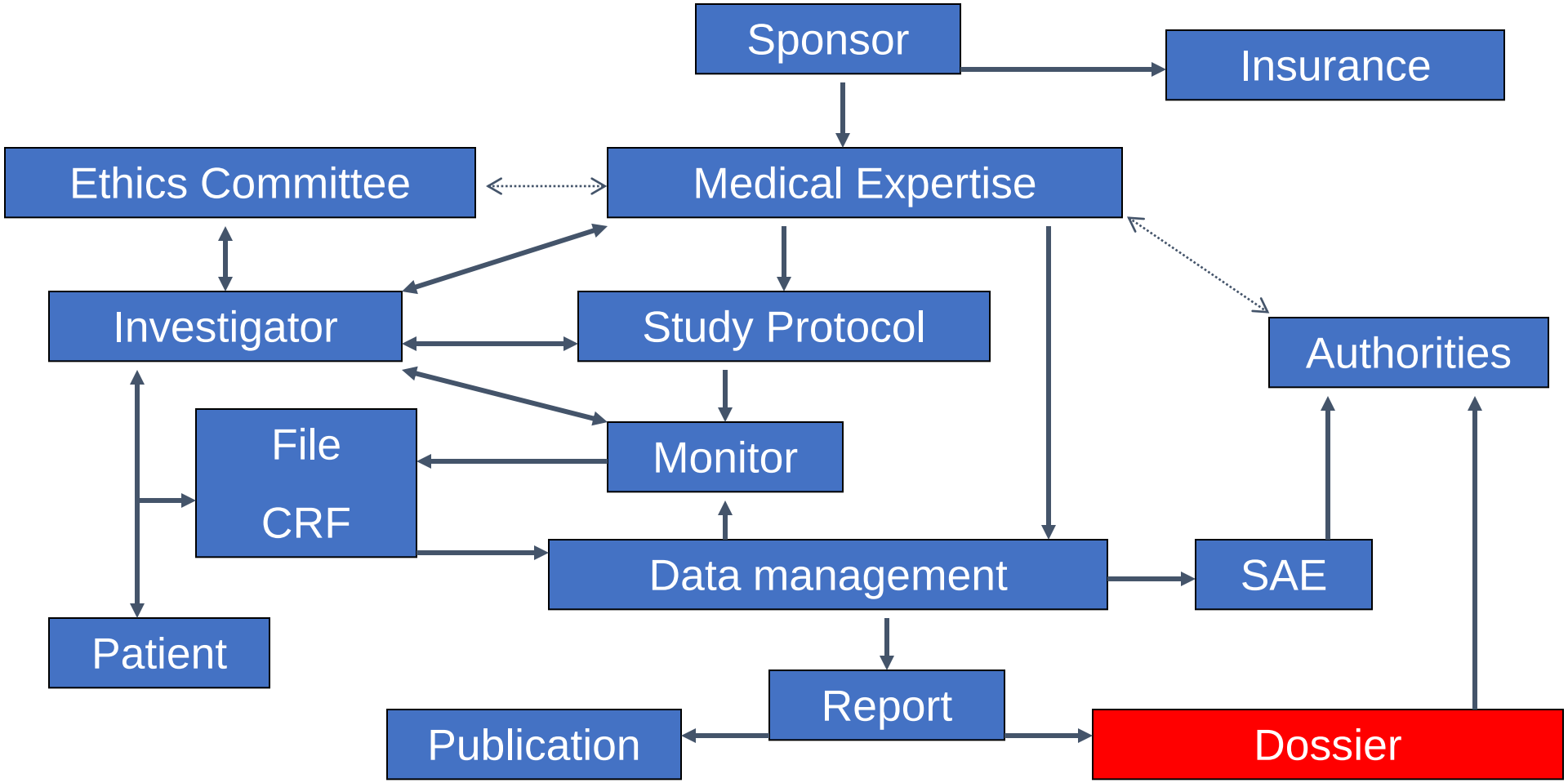


* Composite Figure from Hulstaert et al. Neurology 1999;52:1555-1562

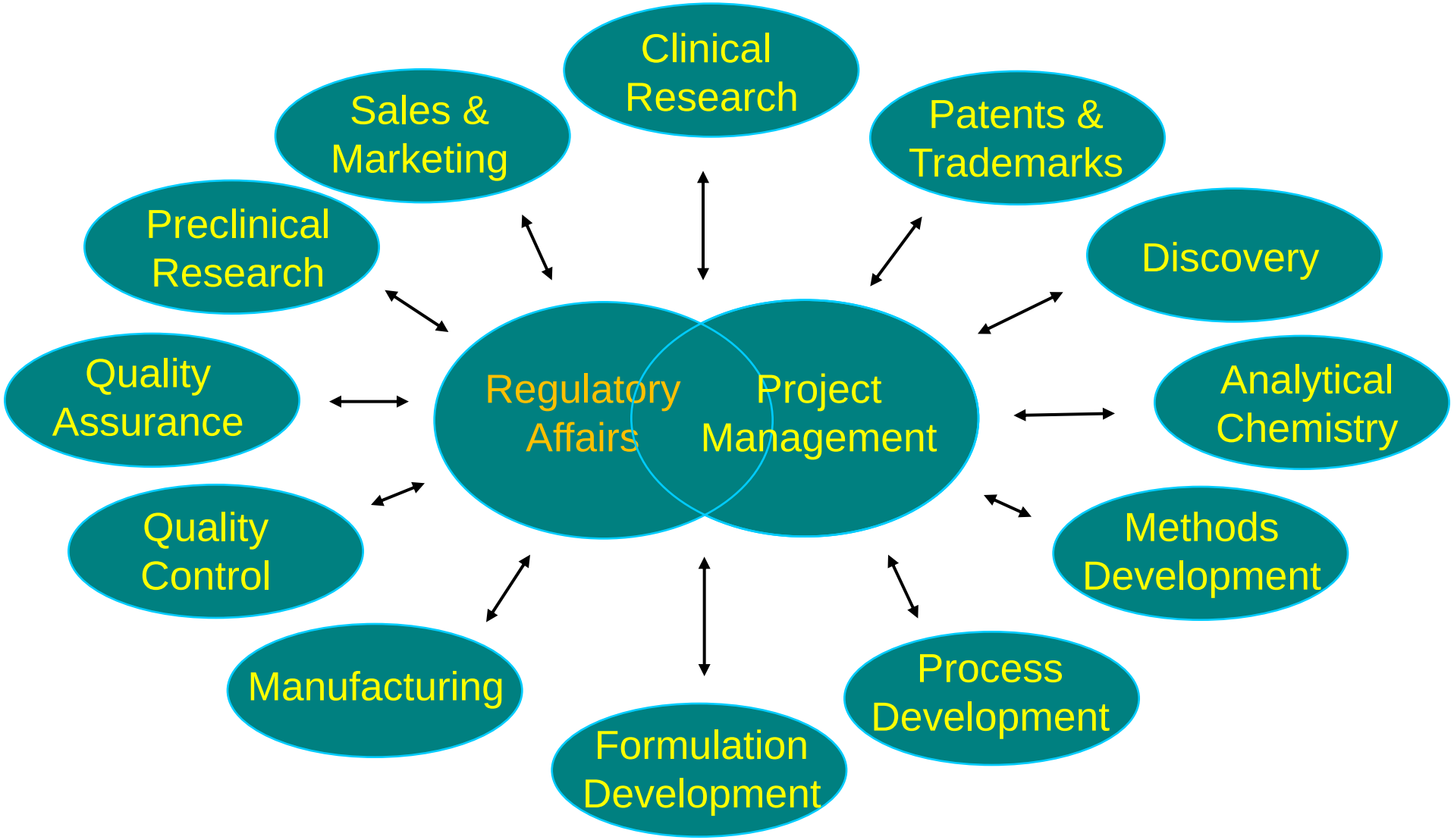
Pharmaceutical projects - success rate

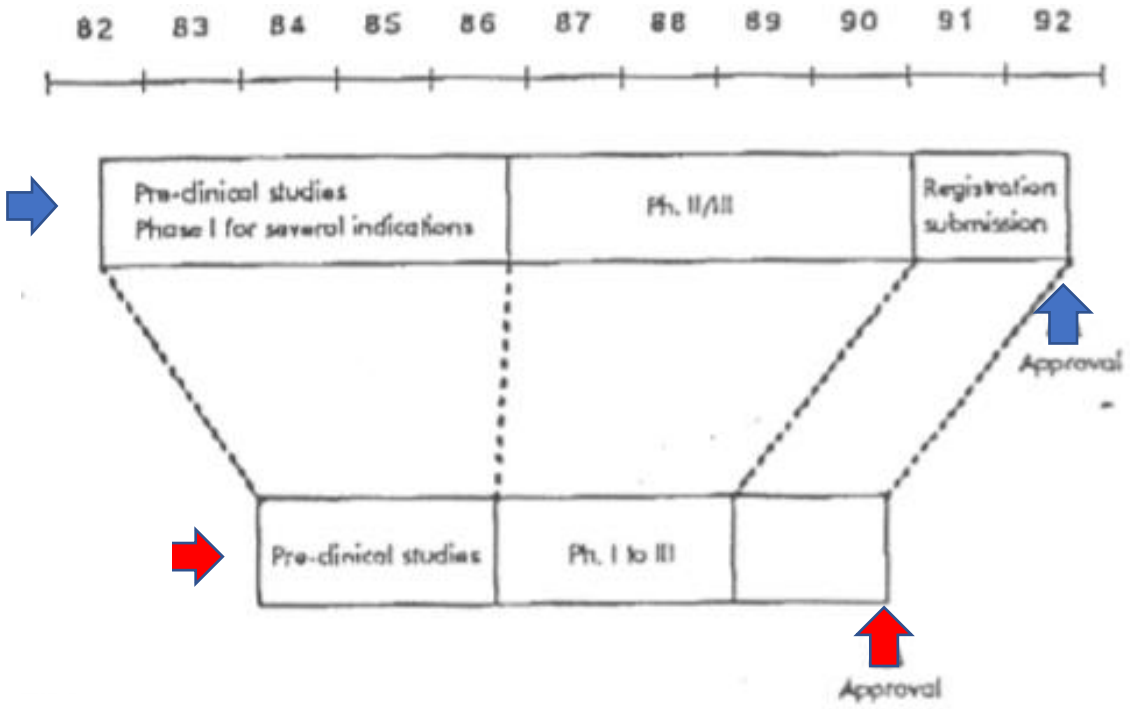


Steps in a Clinical Trial



Drug Development in a Pharmaceutical Company





First to market en marktaandeel

5HT3 receptor antagonisten
tropisetron versus ondansetron

Nausea en braken

- Chemotherapie
  - bij volwassenen
  - bij kinderen
- Postoperatief
  - Preventie
  - Behandeling
- Radiotherapie

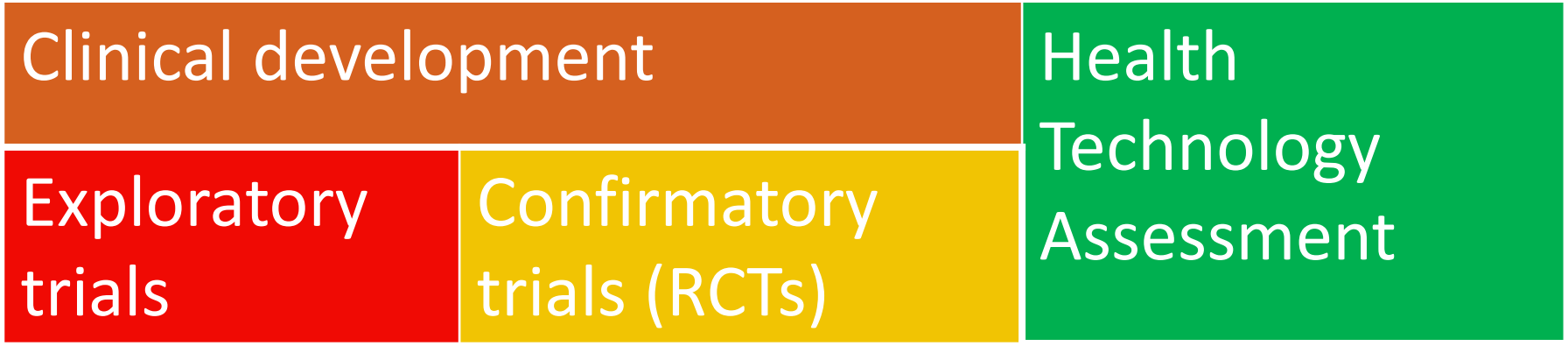
Klinische studies voor registratie bijkomende indicatie tropisetron
Preventie en behandeling van postoperatief braken

- Belang van geregistreerde indicaties voor ziekenhuisformularia
- Fase 2/3 programma in 18 maanden
- Drie klinische studies, meer dan 2000 patiënten
- Expert Rapport voor Wederzijdse Erkenningsprocedure (10 landen)

The Startup Biotech Company

- Beursgenoteerd bedrijf
  - Focus op de technologie eerder dan op medische noden
  - Publieke informatie, verwachtingen
  - De financieel analyst
  - Fail fast versus single product company
- Kwaliteit
  - Academische wereld versus sterk gereguleerde omgeving
  - Expertise in ontwikkeling geneesmiddelen onvolledig
- Tijd
  - Time to market / time to peak sales dikwijls vertraagd door het zoeken van een partner of de noodzaak voor herfinanciering
- Kosten
  - Uitbesteden lukt best als je het domein kent

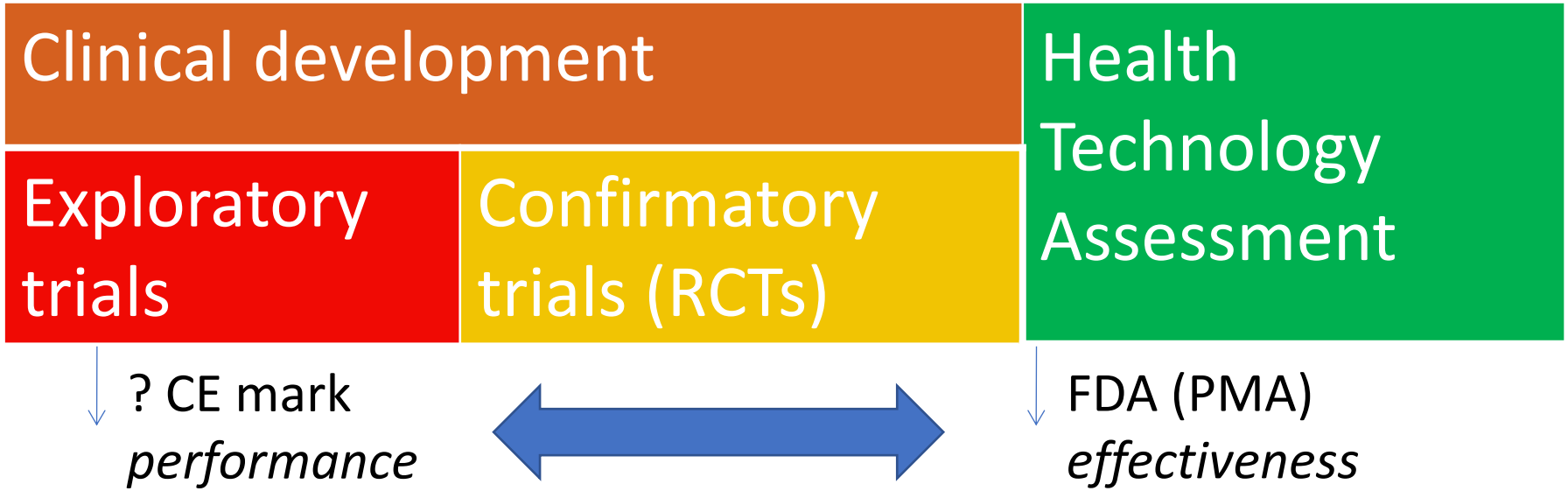
Clinical development and HTA



- internal validity
- safety
- efficacy

- external validity
- comparative effectiveness
- cost-effectiveness
- budget impact

Naar meer klinische studies met medische hulpmiddelen?



Pre-market clinical evaluations of innovative high-risk medical devices in Europe.
Hulstaert F, Neyt M, Vinck I, Stordeur S, Huić M, Sauerland S, Kuijpers MR, Abrishami P, Vondeling H, Flamion B, Garattini S, Pavlovic M, van Brabandt H.
Int J Technol Assess Health Care. 2012 Jul;28(3):278-84.

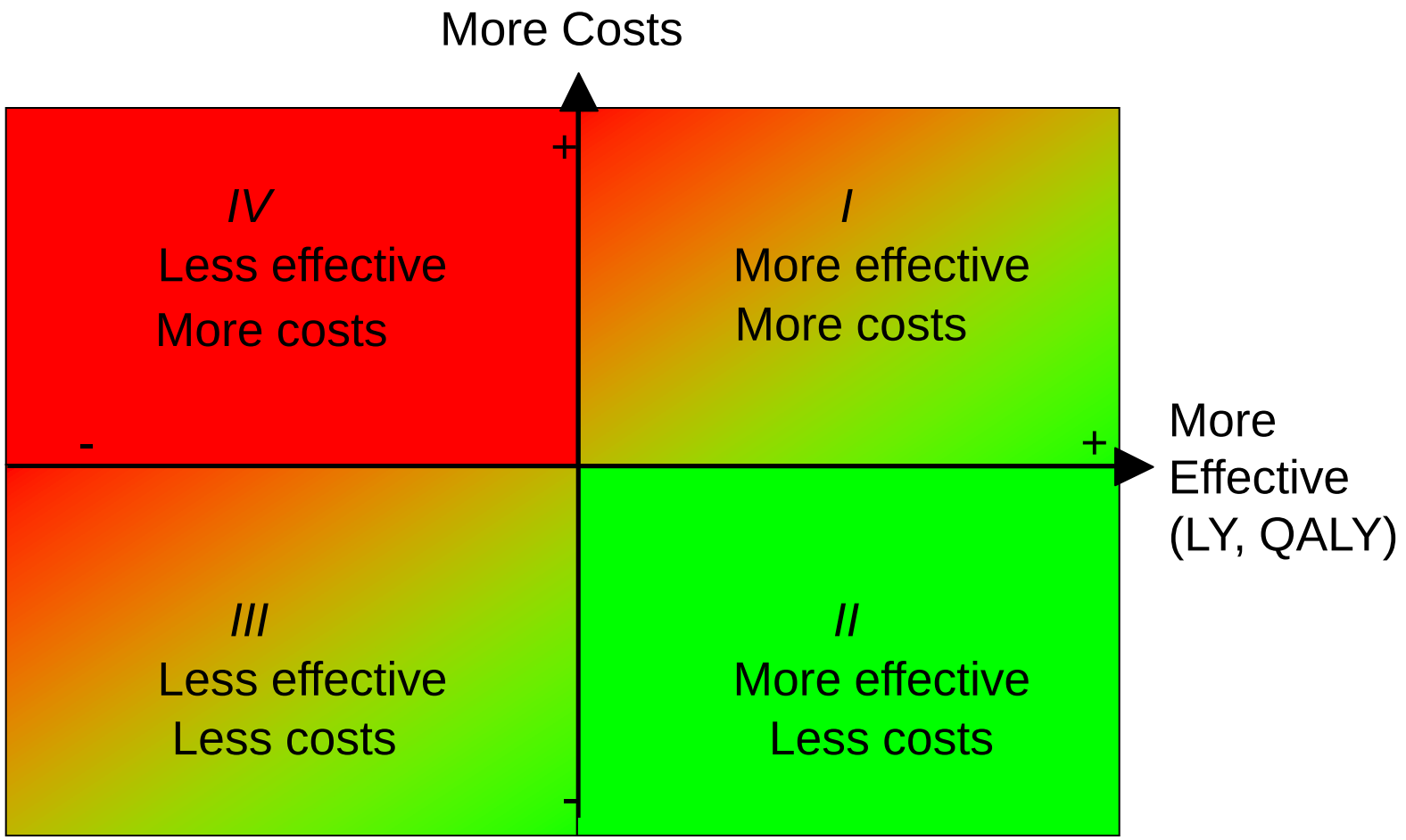
EU Regulation (testaankoop, randomisatie)

Randomised trials balance for the unknown

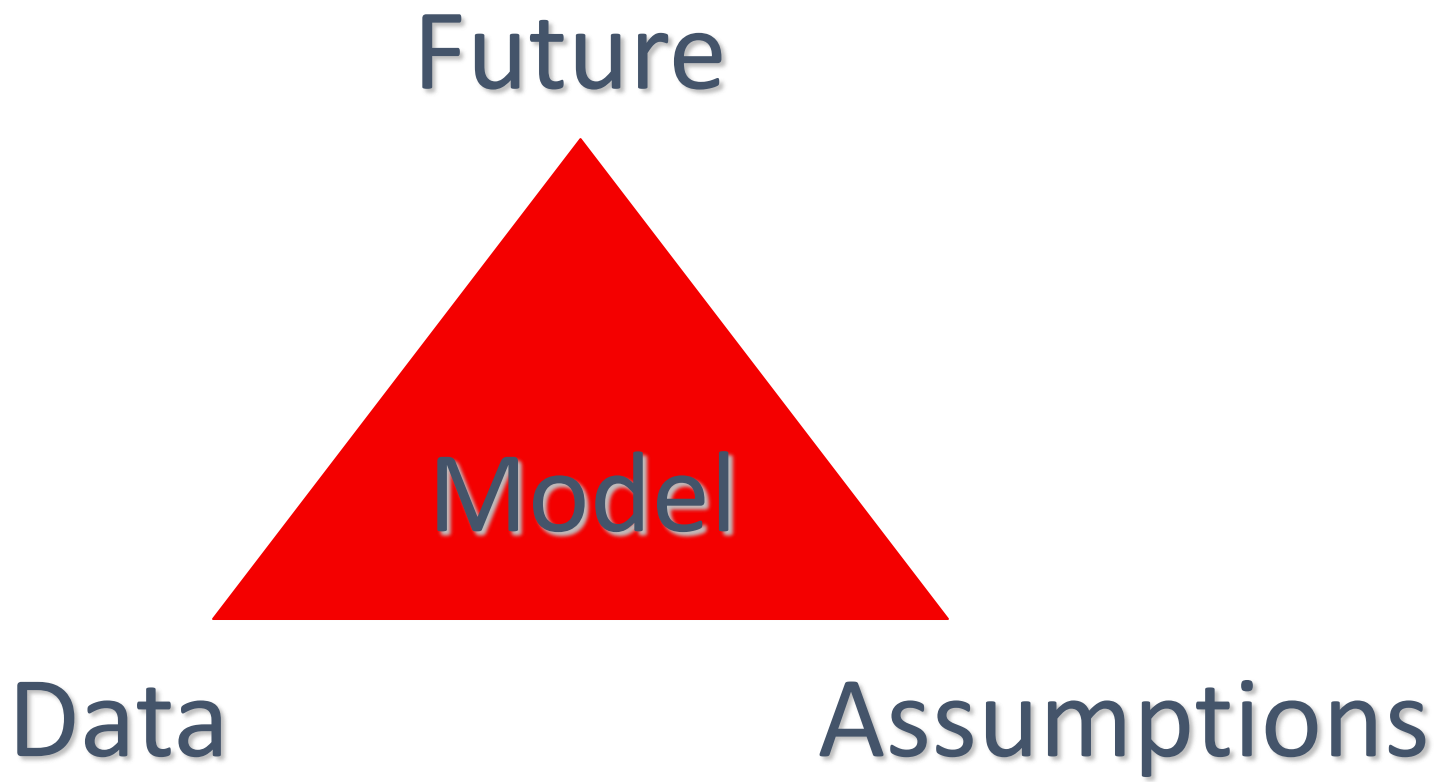
Real-world data are not sufficient - the case of renal denervation

- EU HTA report:
  - "renal denervation using the Symplicity® system appears to decrease blood pressure, whereas the effects of other systems on blood pressure are uncertain."
  - Reimbursed in 13 countries in Europe, and in most cases regardless of the type of device.
- The same day: RCT for FDA: NO EFFICACY, all trials put on hold.

Incremental Cost-Effectiveness Ratio
ICER



How to estimate an Incremental Cost-Effectiveness Ratio (ICER)



Over toegang tot data en gezondheidseconomische modellen;
over ijsbergen, FDA transcripts en luchtfietserij

- Systematische reviews missen nog teveel resultaten; toegang studie rapporten?

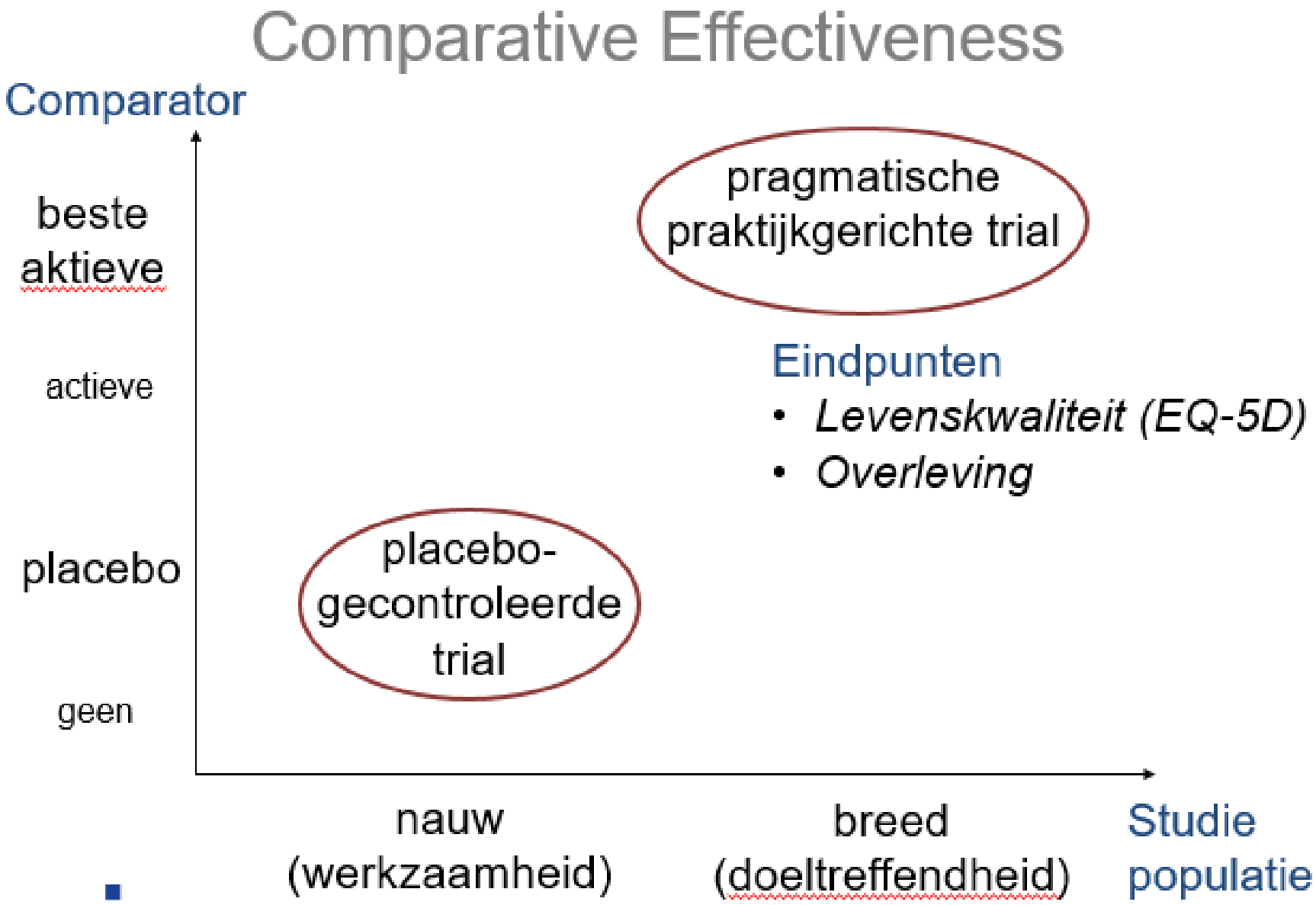
Reporting bias in medical research - a narrative review.
McGauran et al., IQWiG. Trials 2010.

- Trial registries, FDA/CDC website (meeting transcripts), …
- Teveel assumpties in Markov modellen: luchtfietserij
  - HBV-DNA daling en verbetering in kwaliteit van leven

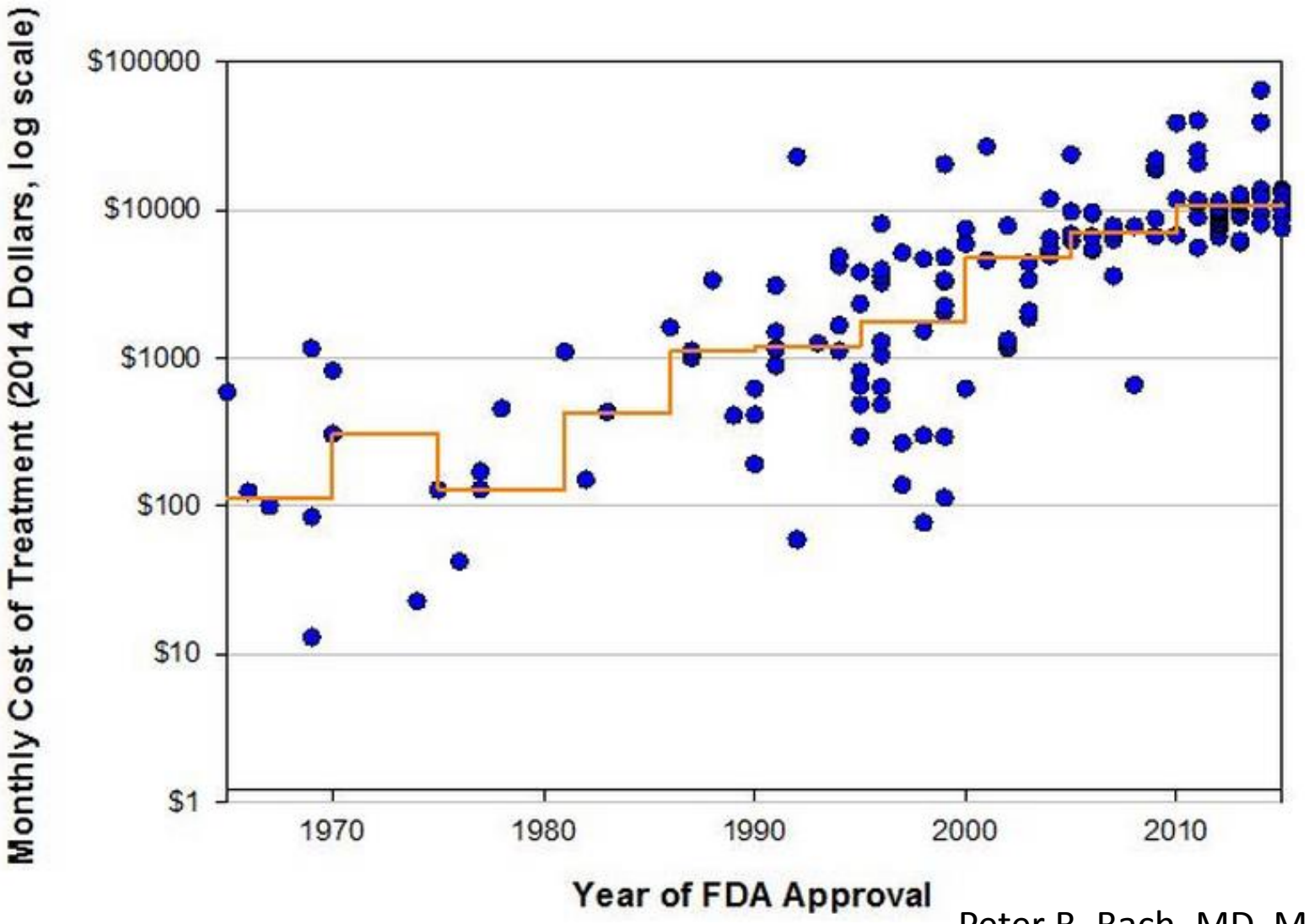
GO/NOGO beslissingen in de medische industrie

- van belang voor de volksgezondheid maar er zijn geen vertegenwoordigers van volksgezondheid bij betrokken
- belang artsen in industrie afgenomen t.o.v. economen en aandeelhouders
- gevolgen voor de gemaakte keuzes:
  - weinig ontwikkelingen volgens medische nood
  - weinig behandelingen voor kinderen
  - keuze van comparator nog frequent placebo
  - geen aantonen van bijkomend nut (… KCE Trials)
  - hoge prijzen (… werkgelegenheid)

Filling the evidence gaps



The increase in new cancer drug costs



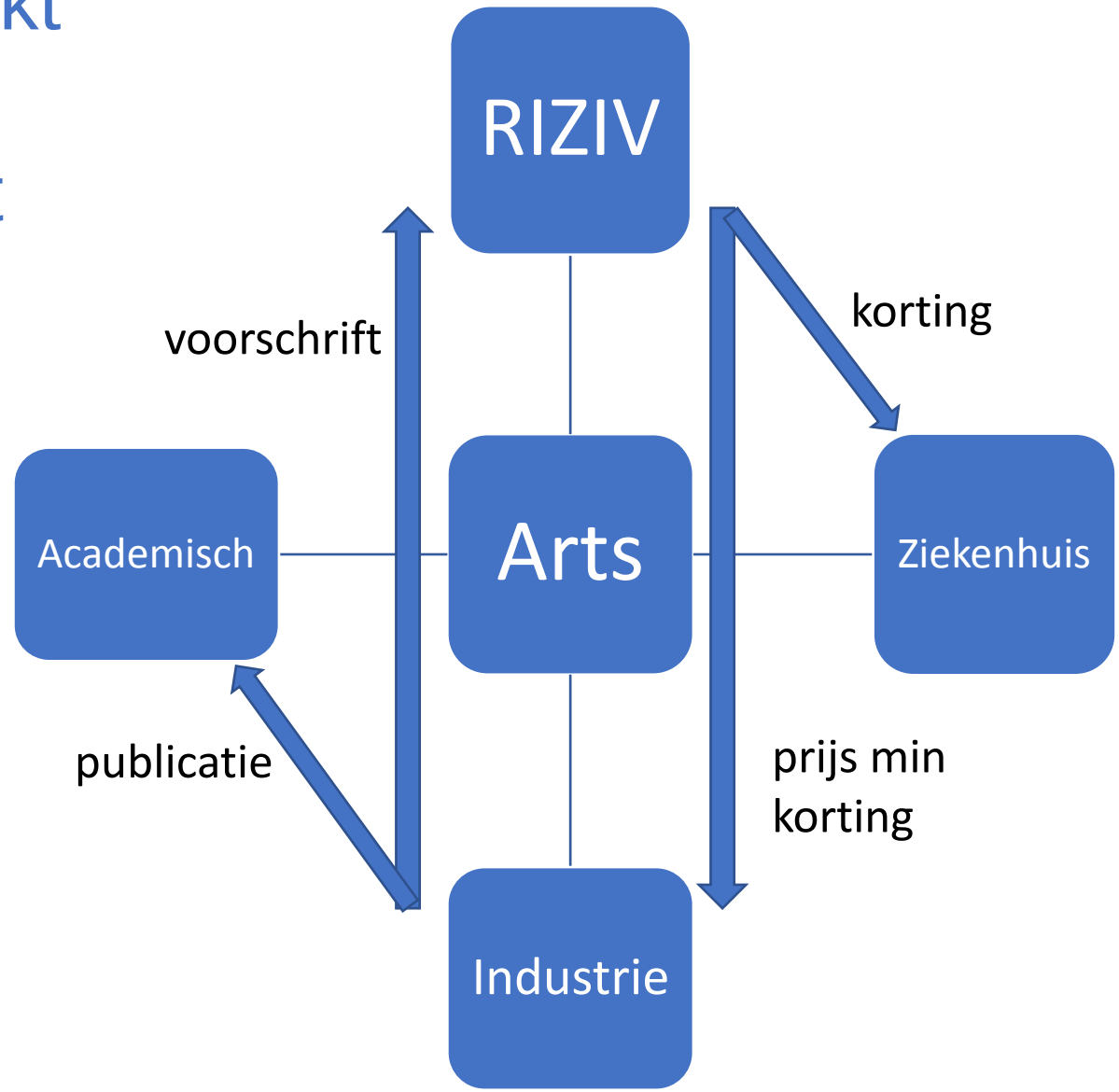
Peter B. Bach, MD, MSKC


Prices for new drugs have significantly increased and are putting a increasing burden on health care budgets in developed nations
The pricing logic is wrong
questions
answers
The drug development system is wrong
The values and principles are wrong

De kostentoxiciteit van nieuwe geneesmiddelen

- Op de agenda van OECD, WHO, G7, G20,.. na sofosbuvir (Sovaldi) voor hep C
- KCE-ZIN scenario development
  - >30 Interviews + two workshops in Amsterdam
  - Investors, economists, payers, regulators, IP specialists, patient representatives, Mario Negri Institute, EORTC, Bill and Melinda Gates foundation, Cochrane Collaboration, policy makers, MIT, Harvard, MSK, pharmaceutical industry, …
- Pistes
  - Geneesmiddelagentschappen publiek gefinancierd
    - Aantonen therapeutische meerwaarde
    - Transparantie, ook voor preklinische data
  - Public Private Partnership/ontwikkeling in de publieke sfeer
  - Verandering, zelfs eliminatie patentsysteem voor geneesmiddelen
  - Ontkoppelen R&D markt van de productie en verkoop
    - Met een beloning na ontwikkeling, generiek vanaf dag 1
  - Compulsory licensing

Verandering lukt slechts als de incentives juist gezet worden.



"Frankly sir, we're tired of being on the cutting edge of technology."