UNIVERSITÄT
HEIDELBERG

“Sprengt die Krebstherapie das Gesundheitssystem?”

Anmerkungen zur Finanzierbarkeit und ökonomischen Logik der onkologischen Therapieforschung & -entwicklung (F&E)

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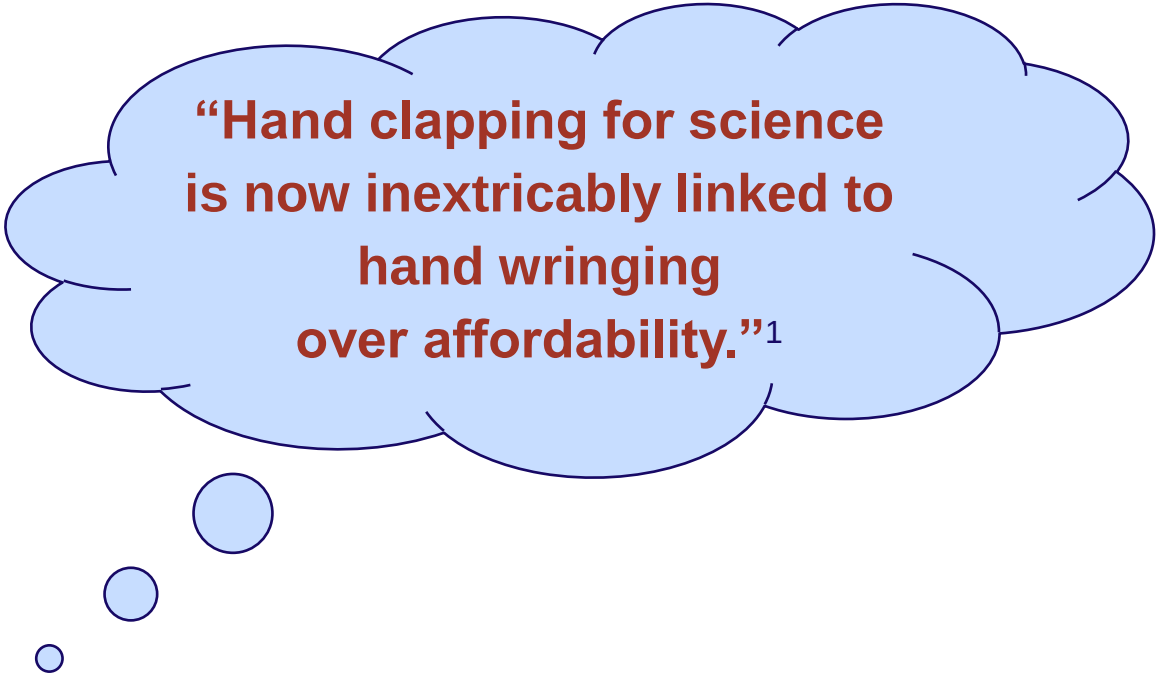
INNOVAL HC
Institute for Innovation & Valuation in Health Care

& Mannheimer Institut für Public Health – www.miph.uni-hd.de

“Sprengt die Krebstherapie das Gesundheitssystem?”

oder:

Können wir uns die moderne Krebsforschung und neue Krebstherapien überhaupt noch leisten?



[1]Peter B. Bach
(Memorial Sloan Kettering Cancer Center, New York, NY):
New Math on Drug Cost-Effectiveness.
New England Journal of Medicine 2015 (November 05); 373 (19): 1797-1799.

1. Medizinische Forschung & Entwicklung (F&E) im Allgemeinen und Krebsforschung im Speziellen ist aufwendig, langwierig, riskant und deshalb teuer.
2. F&E-Aufwand generiert fixe oder sprungfixe Kosten; innovative Krebstherapien können deshalb (in der Regel *zunächst*) nicht billig sein.
3. Den Kosten der Krebsforschung und -therapie müssen ihr Nutzen [*und die volkswirtschaftlichen und humanitären Kosten von Krebserkrankungen(?)*] gegenüber gestellt werden.

“Yes, We Can [Afford It]!”[1]

4. Wachsende Gesundheitsausgaben (folglich auch innovative Krebstherapien) werden auch zukünftig finanzierbar bleiben.
5. Es gibt jedoch einige Voraussetzungen und Handlungsbedarf, um diesen Optimismus belastbar zu machen.

[1]W.J. Baumol: *The Cost Disease – Why Computers Get Cheaper and Health Care Doesn‘t*. New Haven, CT: Yale University Press 2012.

Institutional Background

Who We Are

- Institute for Innovation & Valuation in Health Care (INNOVAL^{HC})
  - **Independent** Not-For-Profit Research Organization (**Not** a Commercial Contract Research Organization)
  - Founded in Aschaffenburg / Germany in June 2005
  - Formally associated with the University of Applied [Economic] Sciences Ludwigshafen
  - Funding of Projects
    - Under an “unrestricted educational grant” policy
    - Supported by National Institutes of Mental Health (NIMH, Bethesda, Md.), National Health and Medical Research Council (NHMRC, Canberra, ACT), Official HTA Institutions (e.g., IQWiG), Physician Organizations (e.g, FMH, KVBaWue) , Sick Funds (e.g., santésuisse, vdek), Research Foundations (e.g., Deutsche Forschungsgemeinschaft, DFG, Swiss Academy of Medical Sciences, SAMW), Pharmaceutical Industry (USA, UK, CH, D, …)
- Chairman: Professor Michael Schlander, M.D., Ph.D., M.B.A.
- Vice-Chairman: Professor Oliver Schwarz, Ph.D.

Institutional Background

What We Do (Overview and Examples)

- Normative Analysis
  - Normative Health Economics and “Empirical Ethics”
  - Evaluation Principles for Rare & Ultra-Rare Disorders
- Health Care Policy Analysis
  - Pharmaceutical Market Regulation
  - “Appraising the Appraisers”
- Health Technology Assessment (HTA)
  - Systematic Reviews and Value Assessments
  - Swiss HTA Consensus Project
- Applied Health Economics
  - Cost Effectiveness Analyses & Modeling
  - Health Economic Methods Development
- Health Care Utilization Research
  - Nordbaden Project (using German administrative data)
- Education, Outreach & Consulting
  - Heidelberg Health Economics Summer School

Conventional Wisdom

(Not So New…)

„Wer leben will, muss zahlen: Die Kostenexplosion und ihre möglichen Auswirkungen.“[1]

“Serious and Unstable Condition: Financing America‘s Hospital Care”[2]

“The Painful Prescription: Rationing Health Care”[3]

[1]W. Krämer (1982)

[2]H.J. Aaron (1991)

[3]H.J. Aaron & W.B. Schwartz (1984)

Pricing of New Drugs (2014)

“Lawmakers and private insurers (who also warn of Sovaldi-induced premium hikes) appear to worry that the price of Sovaldi, multiplied by the millions of Americans who now have hep C, places too heavy a financial burden on the health care system in the short-term. If it does, then the prospect of long-term savings has little appeal.”[1]

[1]http://pointofcontroversy.com/2014/07/19/high-priced-hepatitis-c-drug-sovaldi/

The Most Expensive Drugs in the World[1]

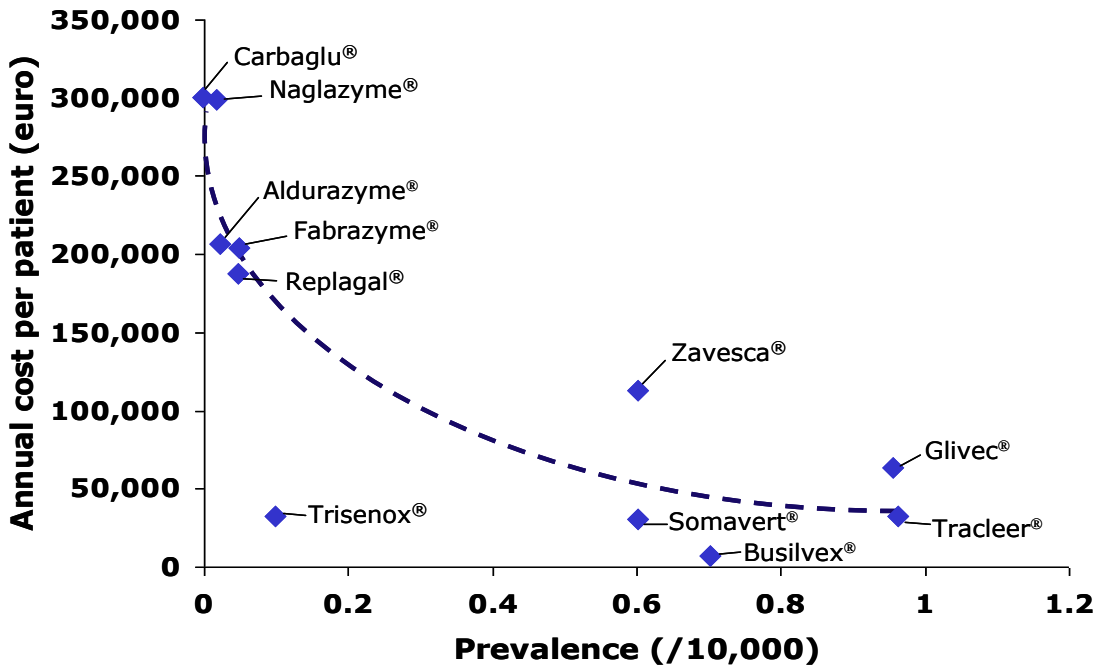
[1]S. Williams, The Motley Fool, June 29, 2013. http://www.fool.com/investing/general... [last accessed Nov. 12, 2015]

The Most Expensive Drugs in the World[1]

1. **Soliris (Alexion)**
   paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS); average annual cost: **US-$ 409,500**
2. **Elaprase (Shire)**
   Hunter syndrome (ERT); **US-$ 375,000** p.a.
3. **Naglazyme (BioMarin)**
   mucopolysaccharidosis (MPS) VI (ERT); **US-$ 365,000** p.a.
4. **Cinryze (ViroPharma)**
   hereditary angioedema (HAE); **US-$ 350,000** p.a.
5. **Myozyme (Sanofi / Genzyme)**
   Pompe disease (ERT); **US-$ 300,000** p.a.

[1]S. Williams, The Motley Fool, June 29, 2013. http://www.fool.com/investing/general... [last accessed Nov. 12, 2015]

Prevalence and Cost per Patient[1]



[1]M. Schlander and M. Beck: *Current Medical Research & Opinion* 2009; 25 (5): 1285-1293

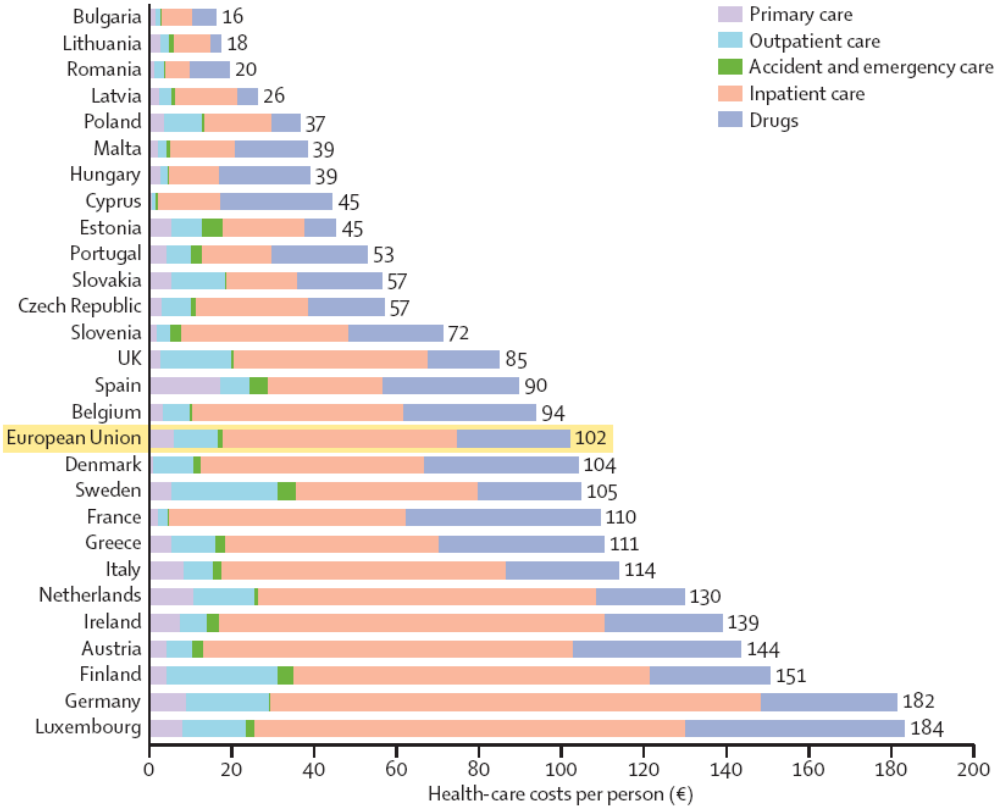
Median Acquisition Costs per Year

Some New Anticancer Drugs[1]

¬ **Nilotinib (Tasigna®)**	**€ 61,600**
¬ **Sunitinib (Sutent®)**	**€ 50,920**
¬ **Cetuximab (Erbitux®)**	**€ 50,120**
¬ Rituximab (MabThera®)	€ 47,200
¬ Sorafenib (Nexavar®)	€ 46,000
¬ Trastuzumab (Herceptin®)	€ 38,200
¬ Bevacizumab (Avastin®)	€ 37,200
¬ Imatinib (Glivec 400®)	€ 36,400
¬ Erlotinib (Tarceva®)	€ 31,080

[1]G. Glaeske et al. (2010)

Cost of Cancer Treatment[1]

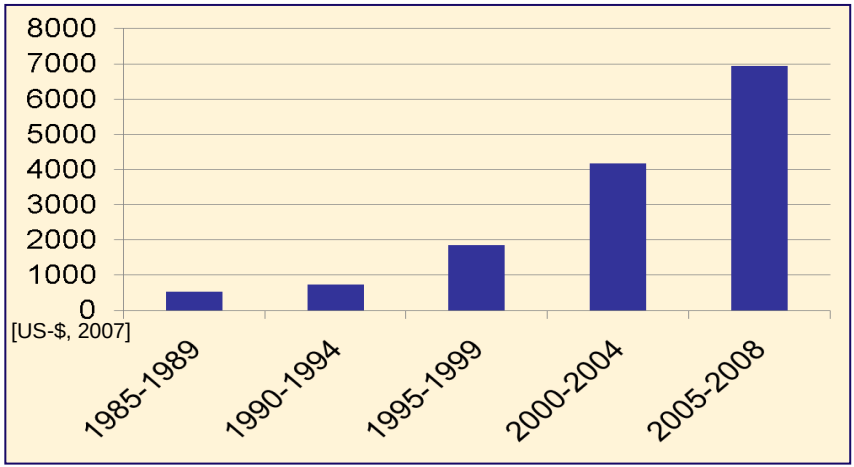


[1]R. Luengo-Fernandez, J. Leal, A. Gray, and R. Sullivan: Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncology* 14; 2013: 1165-1174.

Cost of Cancer Drug Treatment

- Average costs per month of some newer cancer drugs is now US-$ 10,000 to US-$ 30,000 per month.[1]
- Combinations of checkpoint inhibitors cost as much as US-$ 100,000 per month.[1]

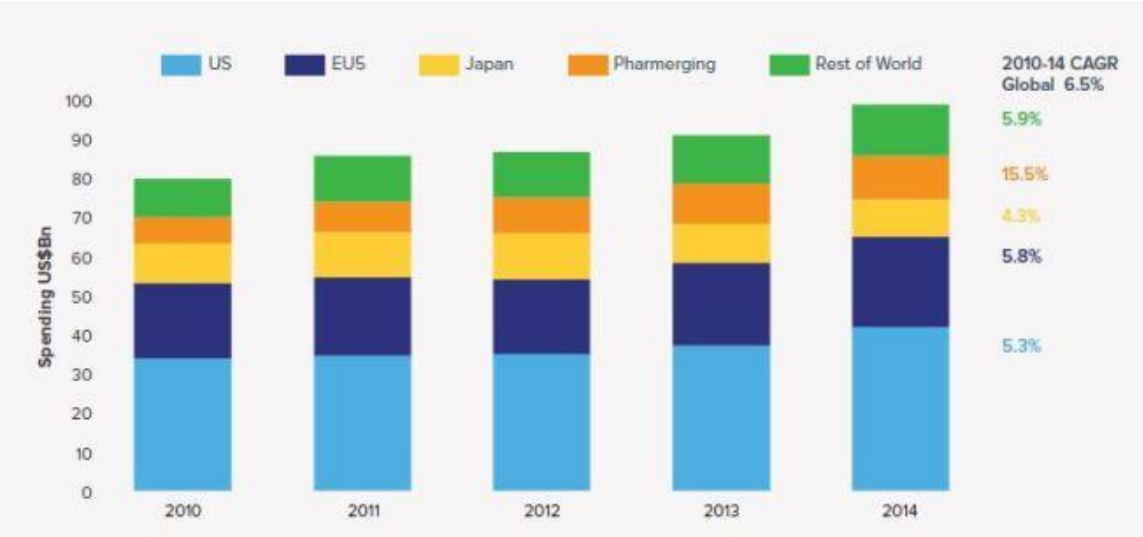
Median Monthly Costs of New Anticancer Drugs
(by Year of Launch[2])



[1]R.C. Young (2015); [2]P.B. Bach (2009)

Cost of Cancer Drug Treatment

Global Oncology Drug Spending 2010-2014[1]



[1]K. Leonard (2015), based on ims data

Cost of Cancer Drug Treatment

Cancer Drug Spending per Capita 2010-2014[1]

[1]K. Leonard (2015), based on ims data

Cost of Cancer Drug Treatment

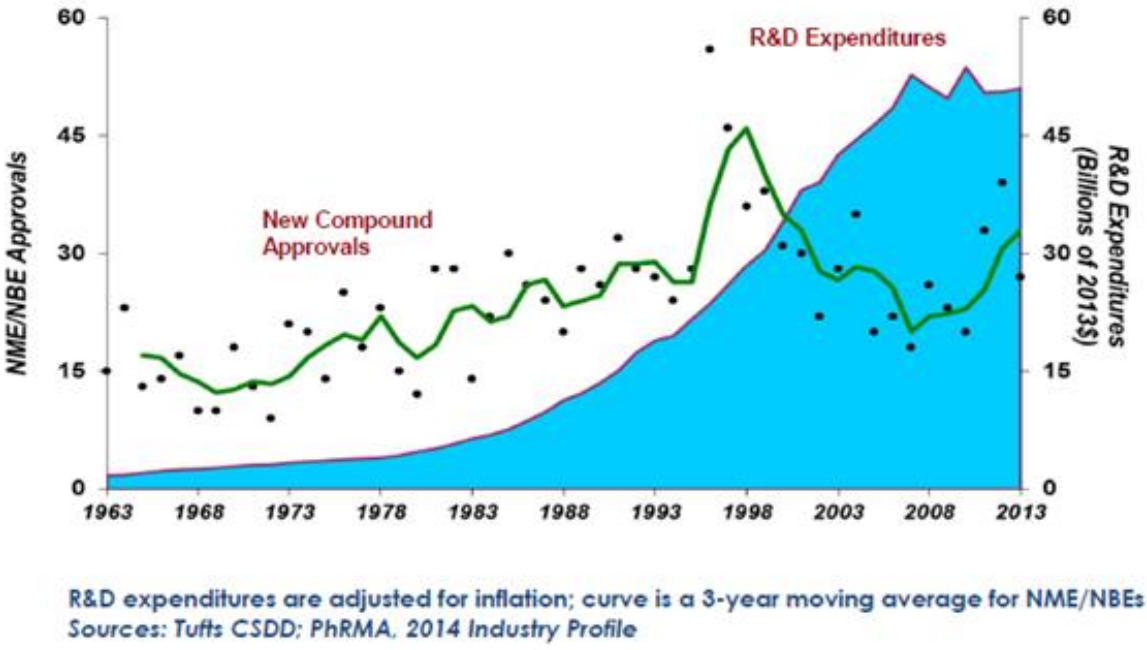
- **Value-Based Cancer Care** (Current *Examples*[1])
  - **Institute of Medicine**: six elements – safety, effectiveness, patient-centeredness, timeliness, efficiency, equity
  - **ASCO**: three elements – clinical benefit (effectiveness), toxicity (safety), cost (efficiency)
  - **NCCN**: "patient-oriented value formula" – efficacy, safety, quality of evidence, consistency of evidence, affordability

- **International Price Comparisons**
  - Germany, Sweden and Switzerland vs. Greece, Portugal, and Spain[2]
  - but: limited to official list prices and by inaccessibility of confidential, discounted price data: "*the end of the international reference pricing system?*"[3]

[1]R.C. Young: Value-based cancer care. *New England Journal of Medicine* 2015 (Dec. 31), 373 (27): 2593-2595.
[2]S. Vogler, A. Vitry, Z.-U.-D. Babar: Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. *Lancet Oncology* 17; 2016: 39-47.
[3]U. Persson, B. Jönsson: The end of the international reference pricing system? *Appl. Health Econ. Health Policy* 2015 (Jun. 26)

Biopharmaceutical R&D:

New Drug Approvals and R&D Spending



Source: J.A. DiMasi. *"Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs"*, Tufts Center for the Study of Drug Development, November (2014). Available: at http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study, s.l.: s.n.

Biopharmaceutical R&D:
Determinants of Fully Allocated R&D Cost / NME

- **Out-of-pocket costs**
  - Clinical development
  - Preclinical research & development
  - Discovery research
- **Clinical success and attrition rates**
- **Capitalization**
  - Development times (“Time-to-Market”, TTM)
  - Cost of capital

NME: New Molecular Entity

Biopharmaceutical R&D:

Overall Success Rates for Clinical Development

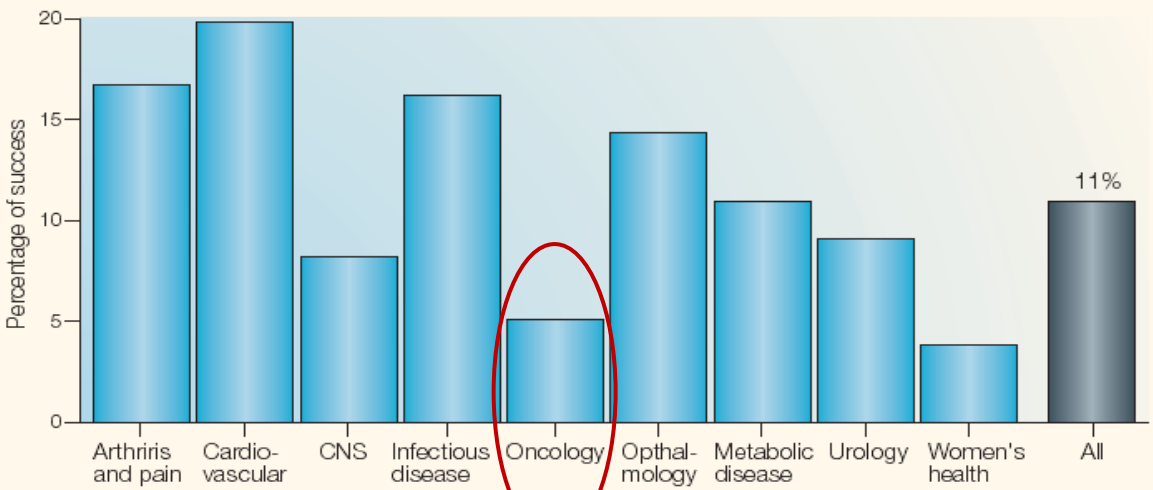


Figure 1 | **Success rates from first-in-man to registration.** The overall clinical success rate is 11%. However, if the analysis is carried out by therapeutic areas, big differences emerge. The data are from the ten biggest drug companies during 1991–2000. (The companies are AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-LaRoche, GlaxoWellcome, Johnson & Johnson, Novartis, Pfizer, Pharmacia, Schering-Plough and SmithKline Beecham; data were obtained by Datamonitor in the Pharmaceutical Benchmarking Study). CNS, central nervous system.

Source: I. Kola and J. LandisC: Can the pharmaceutical industry reduce attrition rates?
Nature Reviews Drug Discovery, August 2004; 3: 711-715.

Biopharmaceutical R&D:
Variables Influencing Clinical Success Rates

- **Therapeutic area:**
  currently best: cardiovascular estimated at 20% on average;
  currently worst: neurology and cancer/oncology at 5-8% on average
- **Compound origin:**
  statistically, self-originated projects carry a higher risk of failure (compared to licensed-in projects)
- **Biologics and biopharmaceutical projects:**
  associated with higher overall success rates (vs. small molecules), but also with longer development times and higher costs of capital
- **Firm size:**
  "Big Pharma" overall success rates slightly lower, but phase III better; development times substantially shorter for Big Pharma
- **Development time:**
  development cost is heavily influence by clinical development time, with cancer projects at 7.6 years (CNS, 10.0y; AIDS antivirals, 5.1y)

Primary data sources:

Office of Health Economics (OHE), London, 2012.

Kola and Landis, *Nature Reviews Drug Discovery* 2004

Abrantes-Metz, Adams and Metz, *Journal of Pharmaceutical Finance, Economics and Policy* 2005

Centre for Medicines Research International (CMR-I), London, 2015

Tufts Center for the Study of Drug Development, Boston, Mass. 2014

Biopharmaceutical R&D:
Attrition Rate and Project Termination Trends

- **Overall success rates** of NMEs entering into clinical development have remained stable, approximately in the 10-25% range.
- **To minimize attrition costs**, it is crucial that unsuccessful NMEs fail as quickly as possible (i.e., before clinical phase III).
- Biopharmaceutical companies have moved to integrate health economics into **early strategic assessments** of NMEs.
- Reasons for premature project termination show a persistent trend to increasing importance of **commercial and economic criteria**.

Biopharmaceutical R&D: Fully Allocated Cost / NME

Study Reference	Sample of New Molecular Entities	Cost of Capital (real)	Discovery Research (included?)	Geography	Estimated cost of R&D [US$m, 2011 prices]
Hansen, 1979	First tested in humans between 1963 and 1975	8%	No	USA	**199**
Wiggins, 1987	1970-1985	8%	No	USA	**226**
DiMasi et al, 1991	First tested in humans between 1970 and 1982	9%	Yes (estimated)	USA	**451**
OTA, 1993	-	-	-	-	**625**
Myers and Howe, 1997	-	-	-	-	**664**
DiMasi et al, 2003	First tested in humans between 1983 and 1994	11%	Yes (estimated)	USA	**1,031**
Gilbert, Henske and Singh, 2003	Estimated first tested in humans between 1995 and 2002	-	Yes	Global	(1995–2000) **1,414** (2000–2002) **2,185**
Adams and Branter, 2006	Drugs entering human clinical trials for the first time 1989-2002	11%	Use DiMasi et al 2003	Global	**1,116**
Adams and Branter, 2010	Drugs entering human clinical trials for the first time 1989-2002	11%	No	Global	**1,560**
Paul et al, 2010	Estimated 1997-2007	11%	Yes	Global	**1,867**
Mestre-Ferrandiz et al, 2012					**1,506**
DiMasi, 2014					**2,600 †**

Adapted from: J. Mestre-Ferrandiz, J. Sussex and A. Towse. *The R&D Cost of a New Medicine*. London: Offiice of Health Economics, Dec. 2012.
†J.A. DiMasi. *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, Tufts Center for the Study of Drug Development (2014).

Biopharmaceutical R&D:
Fully Allocated Cost / NME (2012)

- **most plausible estimate: ~ 1.5 billion US-$**
- **plausible range from 1.1 to 1.9 billion US-$**

while the time, risk, and cost profiles of individual projects may substantially deviate from the average …

… fully allocated economic costs / NME will invariably include opportunity costs (driven by time to market), cost of failures, and non-allocated costs (e.g., discovery research)

- **Effective R&D management** is a critical success factor, making the most important difference between companies, adding or destroying value.

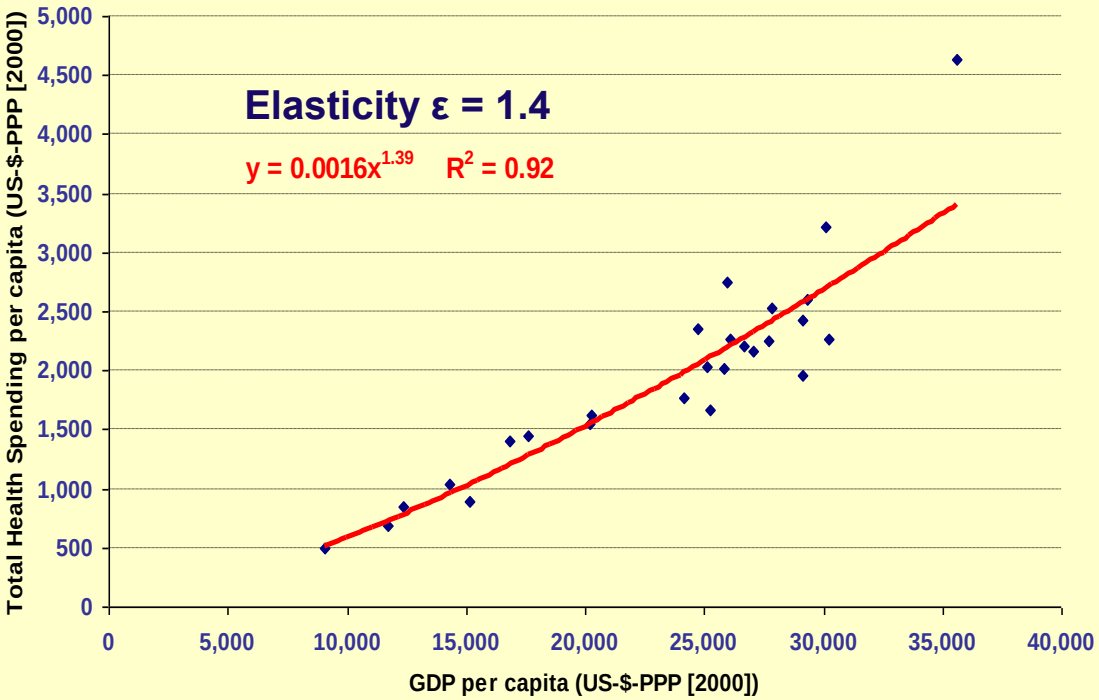
NME: New Molecular Entity

Burden of Disease and Cost of Cancer[1]

- **Burden of Disease** (p.a., EU 2008)
  - **2.45 million people diagnosed with cancer**
  - **1.23 million people died because of cancer**
- **Cost of Cancer** (p.a., EU 2009)
  - **estimated at 126 billion € in total**
  - health care accounting for 40% (i.e., ~51.0 billion €, or 102€ per citizen)
  - productivity loss due to premature deaths ~42.6 billion €
  - productivity loss due to lost working days ~9.43 billion €
  - leading causes of economic cost: lung cancer (18.8 bn €), breast cancer (15.0 bn €), colorectal cancer (13.1 bn €), and prostate cancer (8.4 bn €)

[1]R. Luengo-Fernandez, J. Leal, A. Gray, and R. Sullivan: Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncology* 14; 2013: 1165-1174.

National Income and Health Expenditures[1]



[1]*Cross-sectional* analysis based on OECD Health Data 2002 (26 OECD member states); cf. Kleiman (1974) and Newhouse (1977); from Schlander and Schwarz (2005)

Baumol's Disease (or "Bowen's Curse")[1]

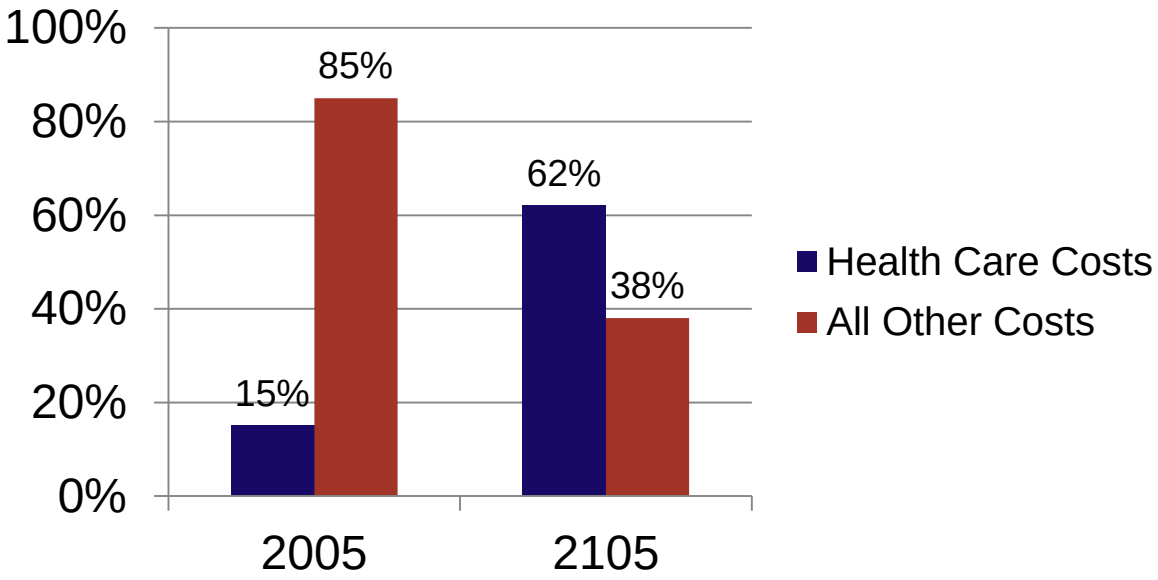
- **"Progressive Sector" of Economy**
  - mass-manufactured products
  - productivity growth as a labor-saving change in a production process
- **"Stagnant Sector" of Economy**
  - personal services
  - health care, education, the live performing arts
  - the quantity of labor required to produce these services is difficult to reduce

[1] W.J. Baumol: *The Cost Disease – Why Computers Get Cheaper and Health Care Doesn't*. New Haven, CT: Yale University Press 2012.

Baumol's Disease:

Health Care and All Other Spending

(extrapolated, as a percentage of U.S. GDP[1])



[1]W.J. Baumol: *The Cost Disease – Why Computers Get Cheaper and Health Care Doesn't*. New Haven, CT: Yale University Press 2012.

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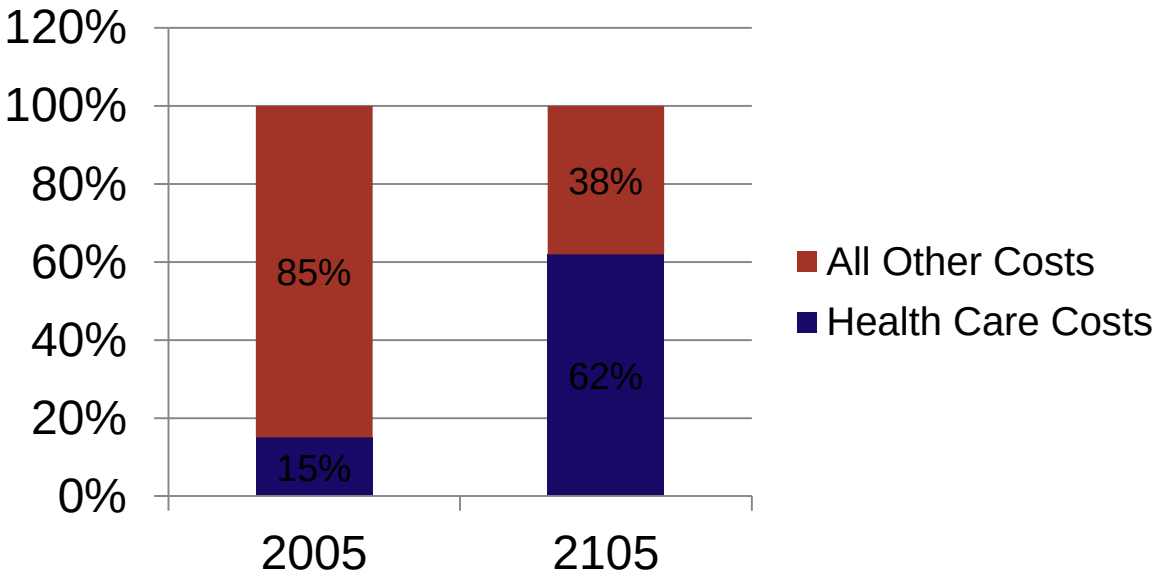
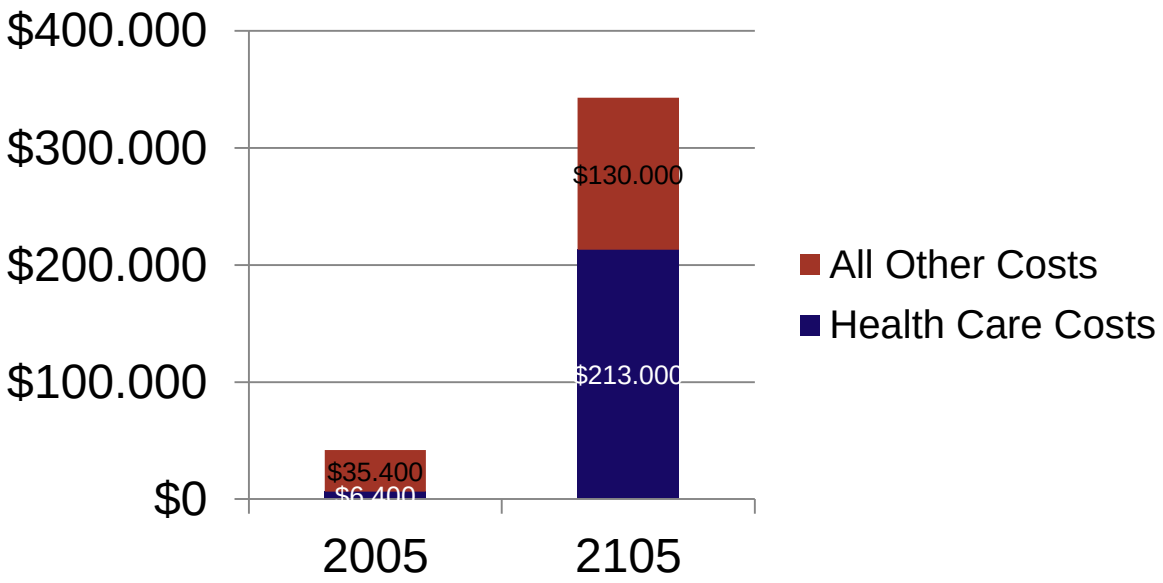


[1]W.J. Baumol: *The Cost Disease – Why Computers Get Cheaper and Health Care Doesn't*. New Haven, CT: Yale University Press 2012.

Baumol's Disease:

Health Care and All Other Spending

(extrapolated spending per capita[1])

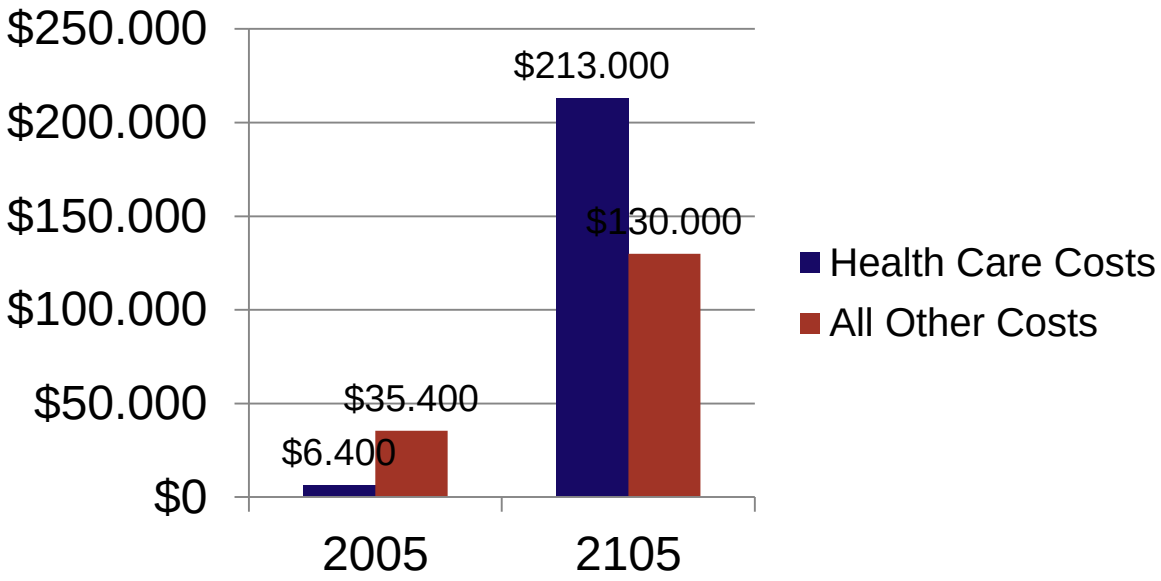


[1]W.J. Baumol: *The Cost Disease – Why Computers Get Cheaper and Health Care Doesn't*. New Haven, CT: Yale University Press 2012.

Baumol's Disease:

Health Care and All Other Spending

(extrapolated spending per capita[1])



[1]W.J. Baumol: *The Cost Disease – Why Computers Get Cheaper and Health Care Doesn't*. New Haven, CT: Yale University Press 2012.

Finanzierbarkeit

Nicht-gesundheitsbezogene Ausgaben als Indikator

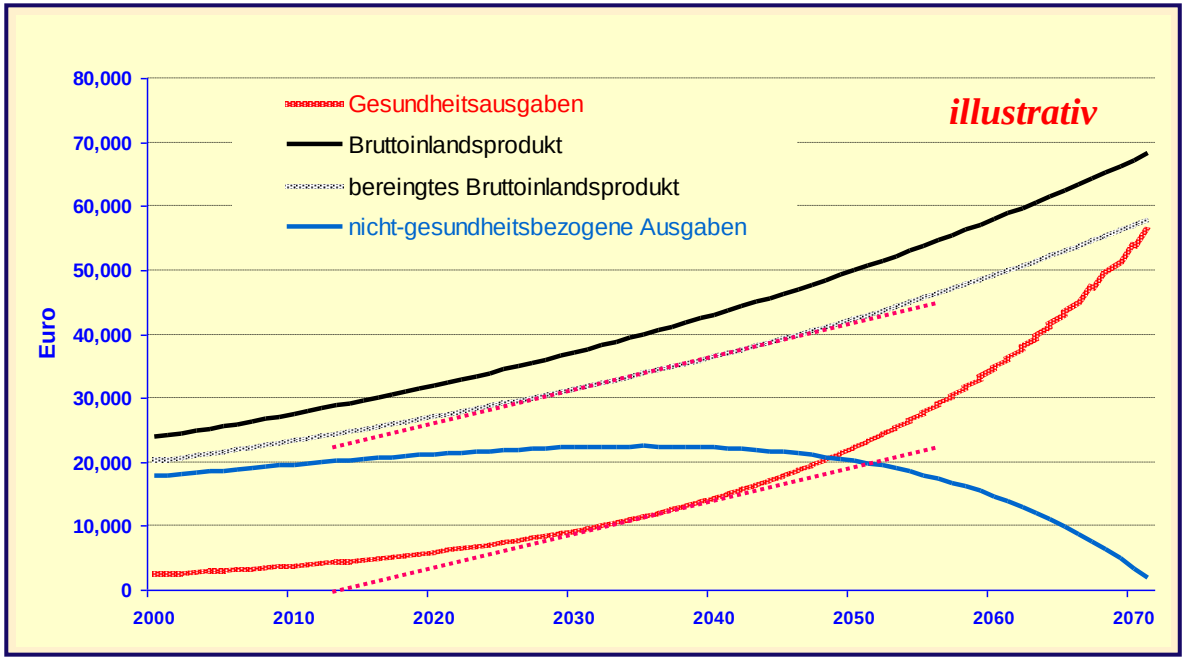
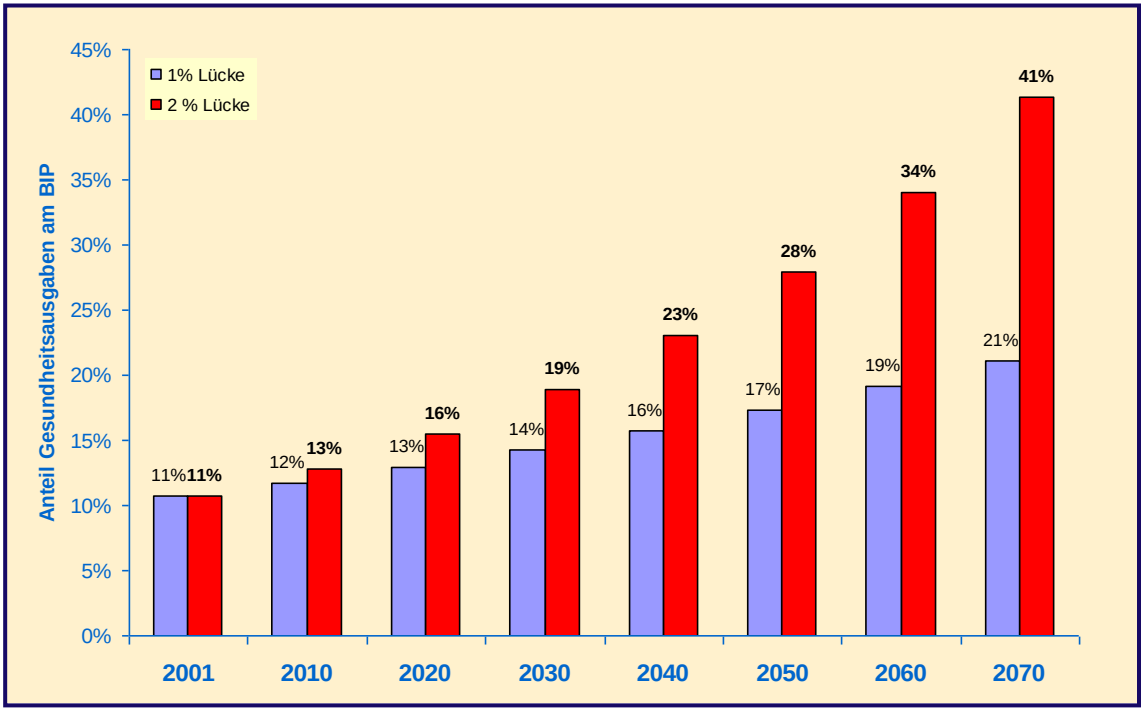


Illustration am Beispiel einer angenommenen Wachstumsrate des Bruttoinlandsprodukts von 1,5% und der Gesundheitsausgaben von 4,5%. Alle Werte pro Einwohner in Preisen von 1995 (BIP Preisindex). Datenquellen: OECD Health Data (2003); Statistisches Bundesamt (2003); eigene Berechnungen. M. Schlander und O. Schwarz (2005).

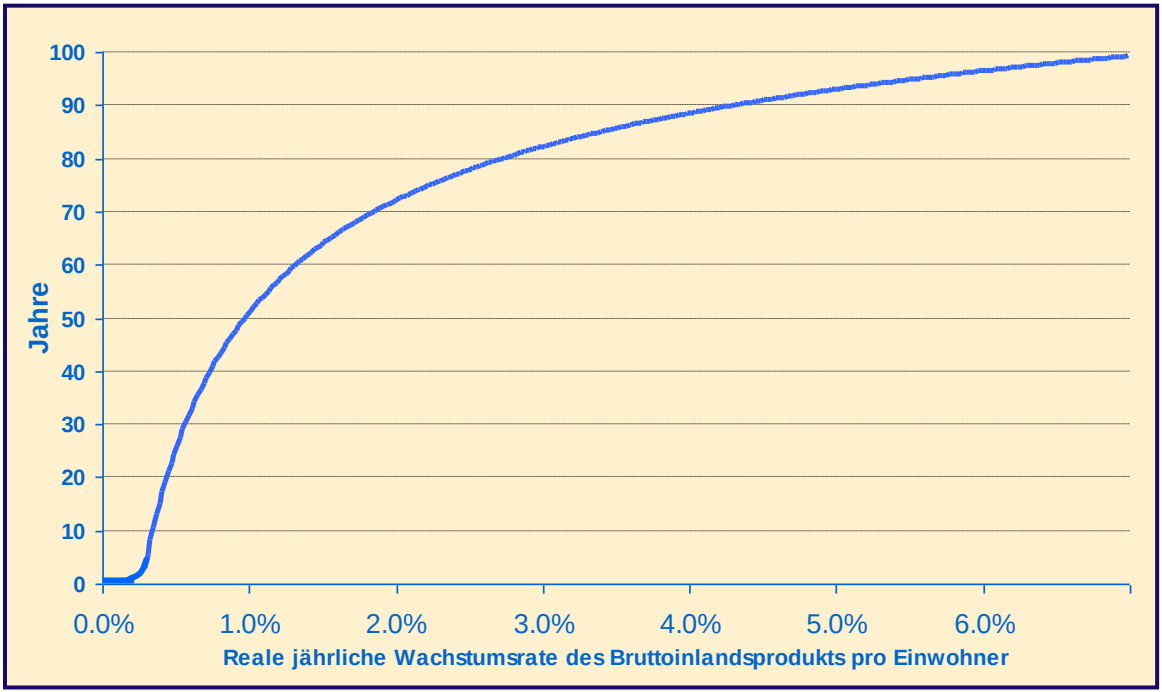
Extrapolation: Gesundheitsausgaben / BIP



Projektion unter der Annahme einer Wachstumslücke zwischen Gesundheitsausgaben und Bruttoinlandsprodukt von einem bzw. zwei Prozentpunkten. Szenario „Fortschreibung“ (BIP-Wachstum 1,2 Prozent). Alle Werte pro Einwohner und Jahr. Datenquellen: OECD Health Data (2003); Statistisches Bundesamt (2003); eigene Berechnungen. M. Schlander und O. Schwarz (2005).

Finanzierbarkeit

und Wirtschaftswachstum (BIP): Sensitivitätsanalyse



Dauer der Finanzierbarkeit in Jahren als Funktion des realen Wachstums des Pro-Kopf-Bruttoinlandsprodukts (unter der Annahme einer konstanten **Wachstumslücke von zwei Prozentpunkten** zwischen den Gesundheitsausgaben und dem Bruttoinlandsprodukt). Datenquellen: OECD Health Data (2003); Statistisches Bundesamt (2003); eigene Berechnungen. M. Schlander und O. Schwarz (2005).

Affordability

(“Yes, but…”)

- **Affordability vs. Financing**
  - equity issues
- **Increasing Public Sector Share of GDP**
  - will productivity continue to accelerate?
- **Educating the Public and Politicians**
  - financial vs. physical measurement of manufacturing output

Affordability

("Yes, but…")

Some Moral (if not Economic) Imperatives:

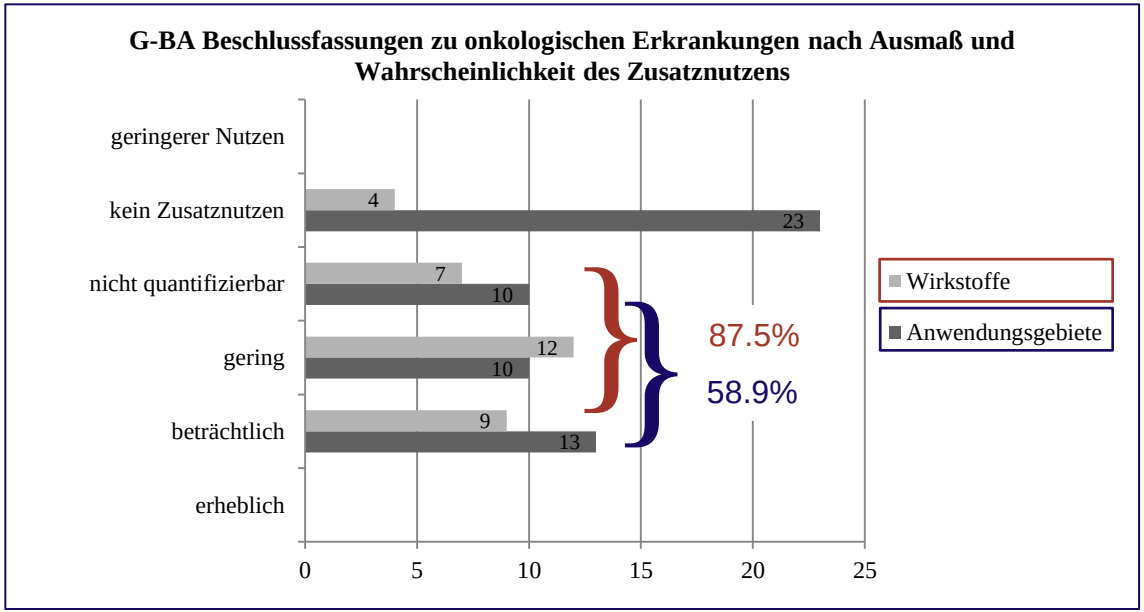
- **Elimination of Ineffective Care**
  - avoidance of harmful or unnecessary interventions
- **Targeting Interventions (including Prevention)**
  - by using genetic information
- **Systematic Health Technology Assessments (HTAs)**
  - ensuring "***Value for Money***"

… searching cost saving alternatives, "choosing wisely",
life style changes, medical education, …

Health Technology Assessment (HTA)

GBA Cancer Drug Appraisals[1]

January 2011 – April 2015 (n=32)



[1]R. Schäfer and M. Schlander (2016); unpublished data and analyses on file at InnoVal[HC], Wiesbaden / Germany.

Health Technology Assessment (HTA)

NICE Cancer Drug Appraisals[1]

January 2011 – April 2015 (n=40)

	Therapeutisches Gebiet: ´Topic Area´	Anzahl Technologien	Anzahl Technologien nach Subgruppen	Nutzenempfehlungen nach Subgruppen		ICER/QALY (Schwellen-werte in Pfund)
				Empfehlung	keine Empfehlung	
Onko-logische Erkrank-ungen	Cancer	29	29	1		< 20.000
				4		20.000 - 30.000
				6	16	> 30.000
				2	52.5%	n.a.
	Blood and immune system conditions	8	11	2		< 20.000
				3		20.000 - 30.000
				3	3	> 30.000
						n.a.

[1]R. Schäfer and M. Schlander (2016); unpublished data and analyses on file at InnoVal[HC], Wiesbaden / Germany.

Health Technology Assessment (HTA)

NICE and GBA New Technology Appraisals[1]

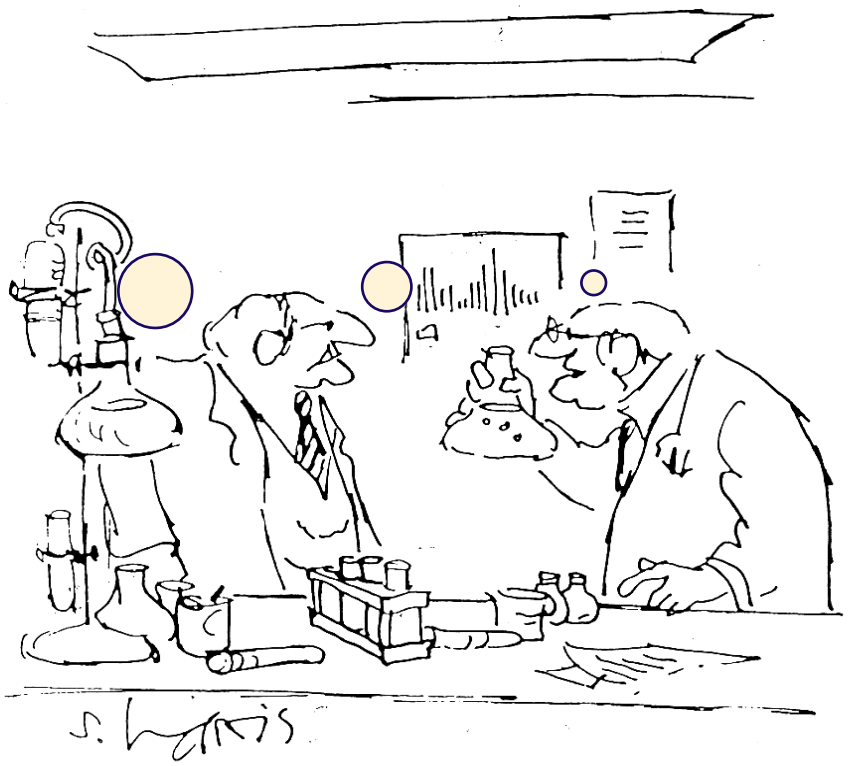
Pairwise Comparison, January 2011 – April 2015 (n=37)

Therapeutisches Gebiet	Anzahl	G-BA Beschluss: Zusatznutzenbeschluss		NICE Guidance: Nutzenempfehlung	
		+	-	+	-
Atmungssystem	1	1		1	
Augen	3	1	2	3	
Hämatologie/Onkologie	3	2	1	1	2
Herz-Kreislauf	3	3		3	
Infektion	4	3	1	4	
Neurologie	4		4	4	
Onkologie	14	11	3	8	6
Psyche/Alkohol	1		1	1	
Stoffwechsel	3		3	3	
Urogenitalsystem	1		1	1	
Gesamt	37	21	16	29	8
relativer Anteil (%)		57%	43%	78%	22%
Gesamt: Onkologische Erkrankungen*	17	13	4	9	8
relativer Anteil (%)		76%	24%	53%	47%

[1]R. Schäfer and M. Schlander (2016); unpublished data and analyses on file at InnoVal[HC], Wiesbaden / Germany.

Health Technology Assessment (HTA)

“It may well bring about immortality – but it will take forever to test it.”



Thank You for Your Attention!

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