Seminar SPD2 – Medicines for every disease – return on investment vs. unmet clinical needs

Online 23. March 2021

Prof. Dr. Wolf-Dieter Ludwig

Drug Commission of the German Medical Association

Conflict of Interest Disclosure:

No relevant financial relationships to announce

3 Self-assessment questions

- An innovative medicine (OECD definition 2018) should offer greater efficacy, reduced toxicity or both.
  - Yes/No?

- Cardiology and gastroenterology belong to the dominant therapeutic areas among approvals of novel drugs by FDA and EMA in 2019.
  - Yes/No?

- Do pricing of novel drugs depend on relevant patients outcome?
  - Yes/No?

OECD (2018), *Pharmaceutical Innovation and Access to Medicines*, OECD Health Policy Studies, OECD Publishing, Paris.
https://doi.org/10.1787/9789264307391-en

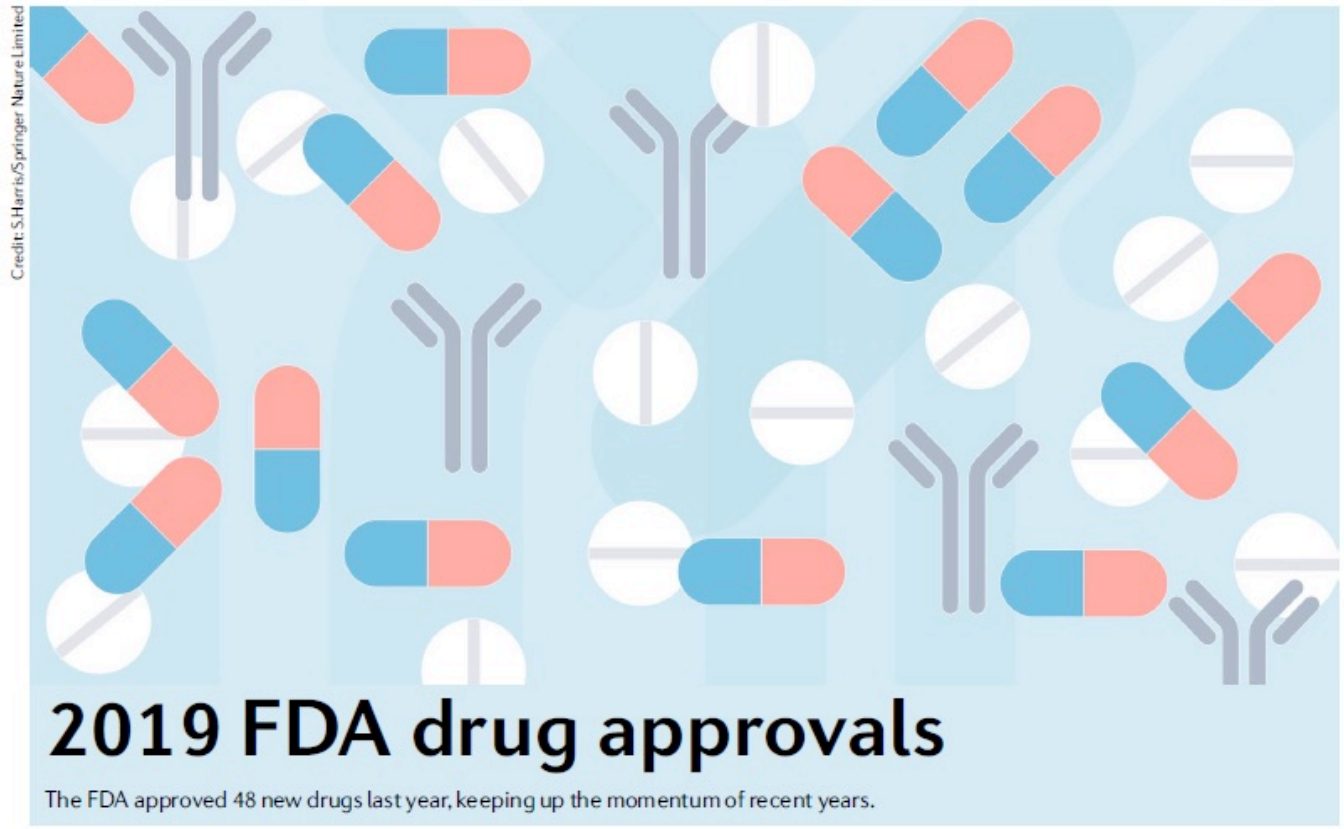
Box 1.1. What is an innovative medicine?

"Innovative" and "innovation" are widely used terms but are rarely defined explicitly. For the purposes of this report a medicine may be described as innovative if it:

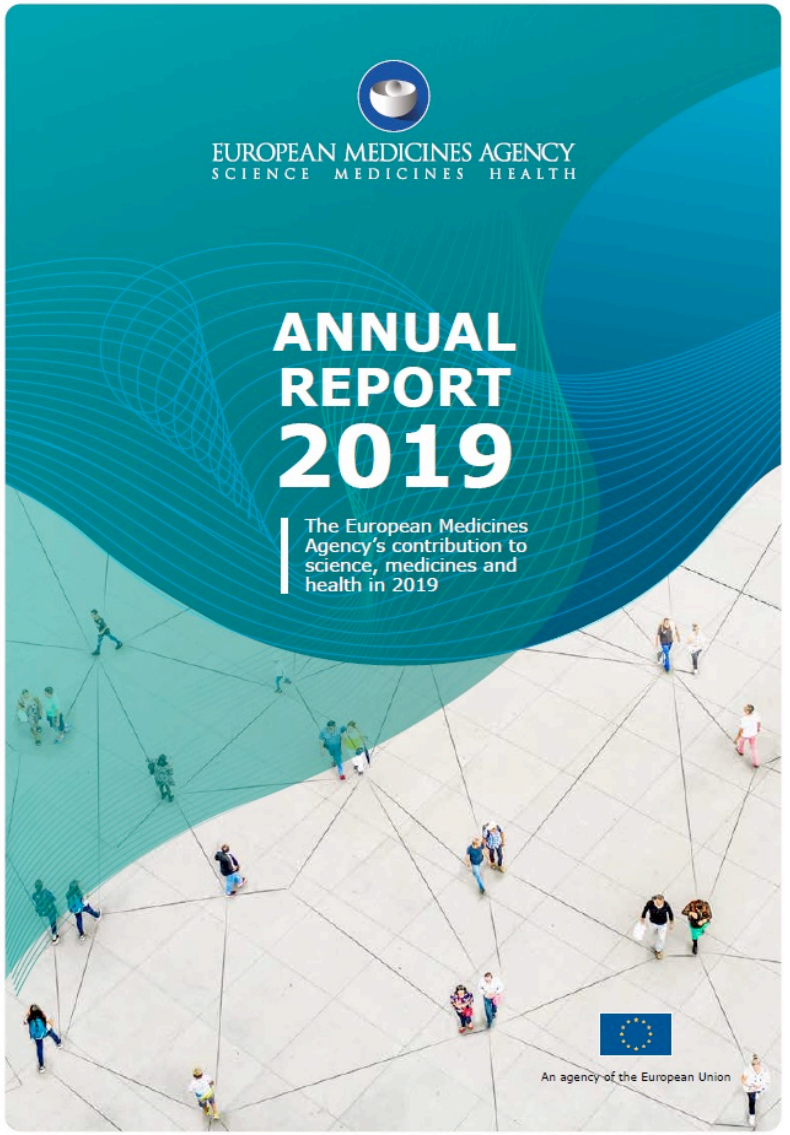
- meets a previously unmet or inadequately met, substantive (i.e. non-trivial) health need
- offers enhanced effectiveness (e.g. greater efficacy, reduced toxicity or both) or other incremental benefit (e.g. a substantive improvement in patient convenience) relative to existing therapeutic alternatives.

Conversely, a product that is new or novel, but does not offer additional benefit over existing therapies would not *per se* be considered innovative (Morgan, Lopert and Greyson, 2008; Bruen et al., 2016).

Approvals of novel drugs by FDA and EMA in 2019



NATURE REVIEWS | DRUG DISCOVERY VOLUME 19 | FEBRUARY 2020 |



Novel FDA approvals since 1993

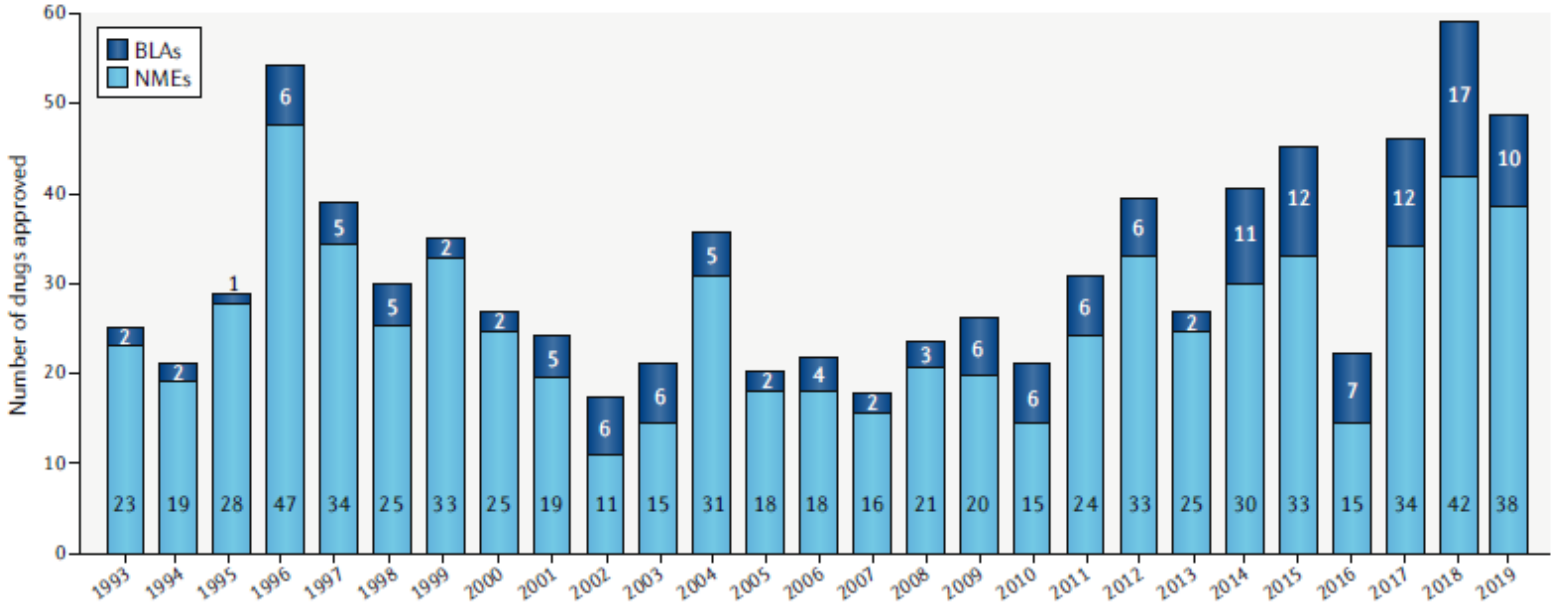
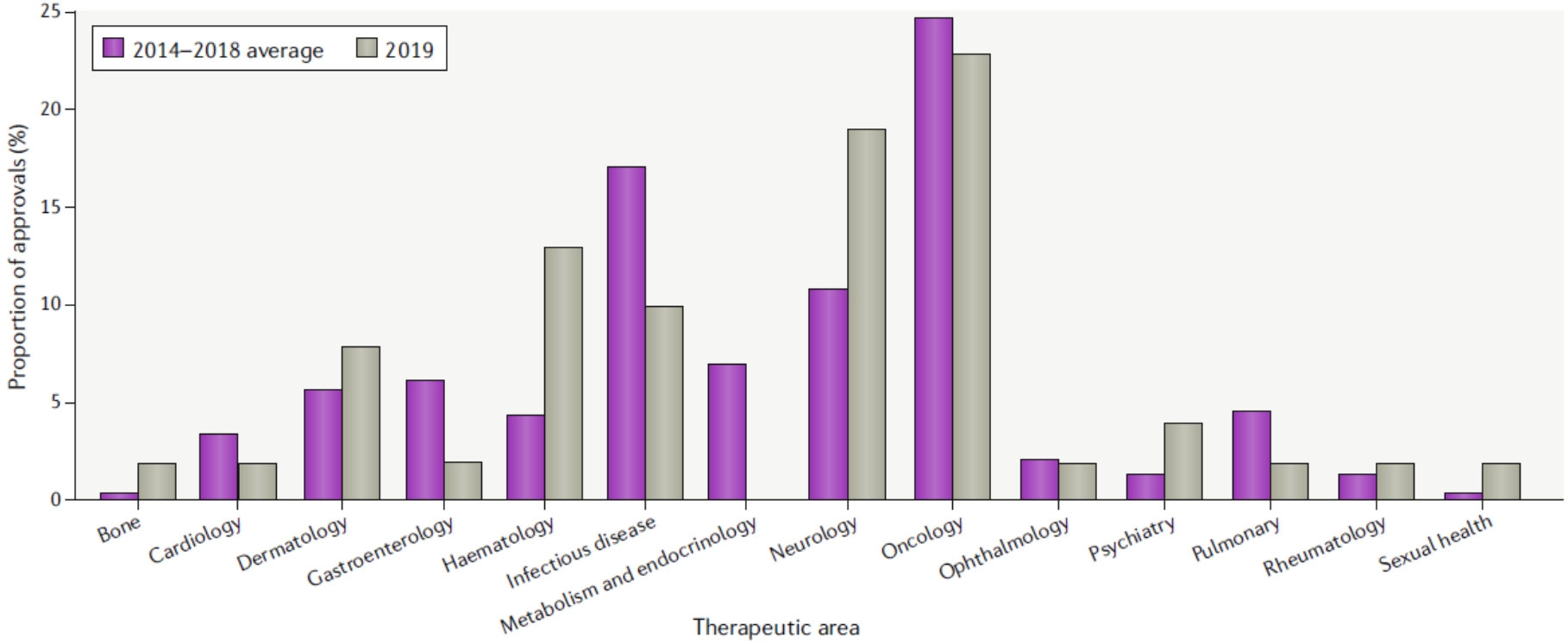


Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See TABLE 1 for new approvals in 2019. Approvals of products such as vaccines and gene therapies by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count (see TABLE 2). Source: Drugs@FDA.

N=28 (58%) priority review products
(expected to offer significant improvements over standards)
N=21 (44%) with orphan drug designation
(rare diseases that affect > 200,000 people in the USA)

Center for Drug Evaluation and Research (CDER): Approvals 2019 by selected therapeutic areas



Cancer dominant therapeutic area (N=11, 23%)

Neurological products (N=9, 19%)

Hematology products (N=6, 13%)

Infectious disease products (N=5, 10%)

ARZNEIMITTELKOMMISSION DER DEUTSCHEN ÄRZTESCHAFT

Outcome of initial evaluation ● PRIME ● ATMP ● Orphan medicine ● Accelerated assessment ● Conditional marketing authorisation ● Approval under exceptional circumstances ● Biosimilar

Medicines recommended for approval

Haematology/ Haemostaseology

Arsenic trioxide Accord
Azacitidine Accord
Azacitidine Celgene
Bortezomib Fresenius Kabi
Deferasirox Accord
Deferasirox Mylan
Doptelet
Esperoct
Grasustek
Ivozall
Polivy
Tavlesse
Ultomiris
Xospata
Xromi
Zynteglo

Infections

Atazanavir Krka
Dectova
Dovato
Posaconazole Accord
Posaconazole AHCL
Quofenix
Recarbrio
Trogarzo

Cancer

Libtayo
Lorviqua
Pazenir
Talzenna
Vizimpro
Vitrakvi

Novel EMA approvals in 2019

Neurology

Ajovy
Epidyolex
Inbrija
Lacosamide UCB
Mayzent
Striascan

Endocrinology

Baqsimi
Isturisa
Evenity
Qtrilmet
Zynquista

Immunology/ Rheumatology/ Transplantation

Amsparity
Idacio
Kromeya
Pegfilgrastim Mundipharma
Rinvoq

N=30

Cardiovascular

Ambrisentan Mylan
Clopidogrel/Acetylsalicylic acid Mylan
Giapreza
Ondexxya

Psychiatry

Dexmedetomidine Accord
Sixmo
Spravato
Sunosi

Uro-nephrology

Febuxostat Krka
LysaKare
Senstend

N = 12 Oncology/Hematology

Dermatology

Nuceiva
Skyrizi

Metabolism

Palynziq
Waylivra

Ophthalmology

Beovu
Rhokiinsa

N= 7 Orphan Drugs

Hepatology/ Gastroenterology

Cufence

Pneumology/ Allergology

Temybric Ellipta

Vaccines

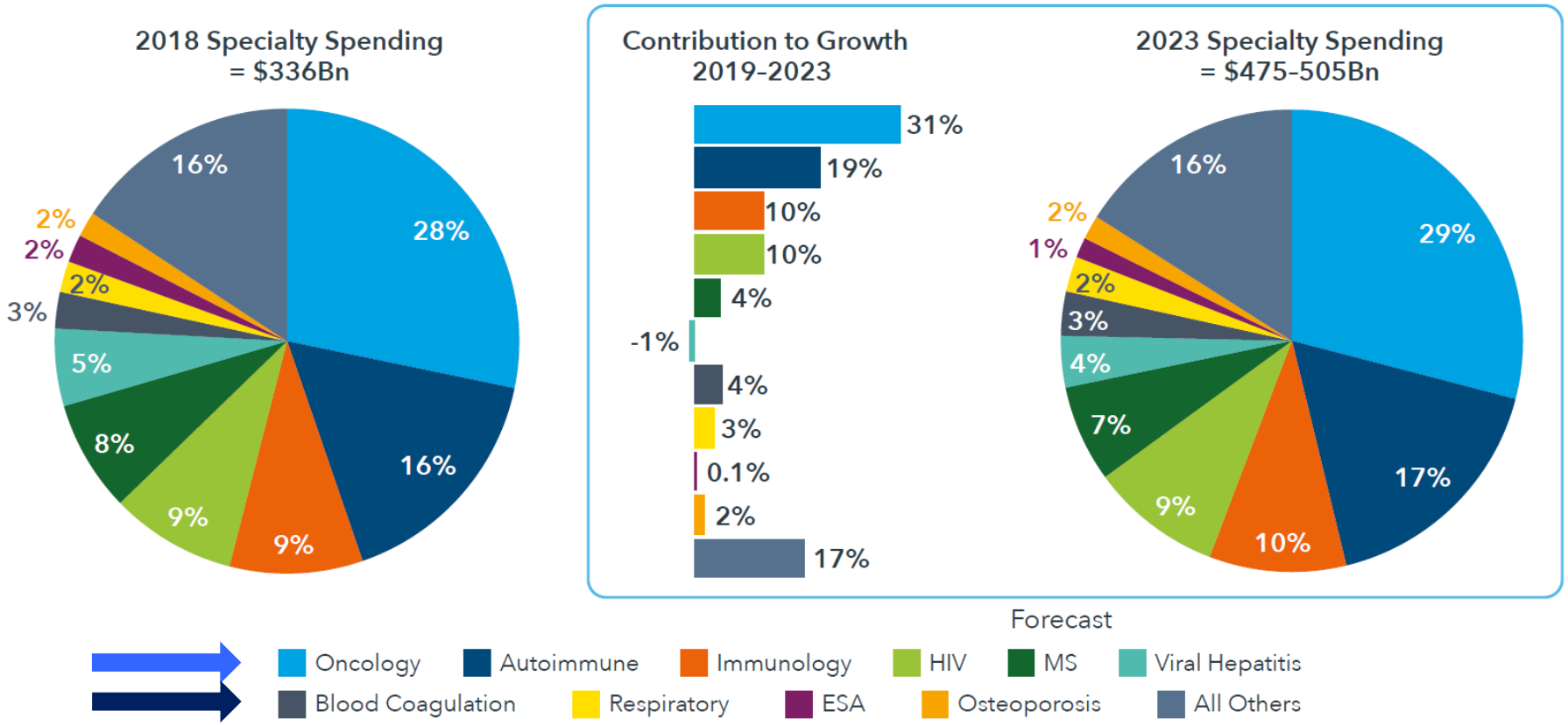
Ervebo

The IMS Institute is now the IQVIA™ INSTITUTE for Human Data Science

The Global Use of Medicine in 2019 and Outlook to 2023

Forecasts and Areas to Watch

2014: 100 Billion US $
2019: 174 Billion US $



New drugs: where did we go wrong and what can we do better?

More than half of new drugs entering the German healthcare system have not been shown to add benefit. **Beate Wieseler** and colleagues argue that international drug development processes and policies are responsible and must be reformed

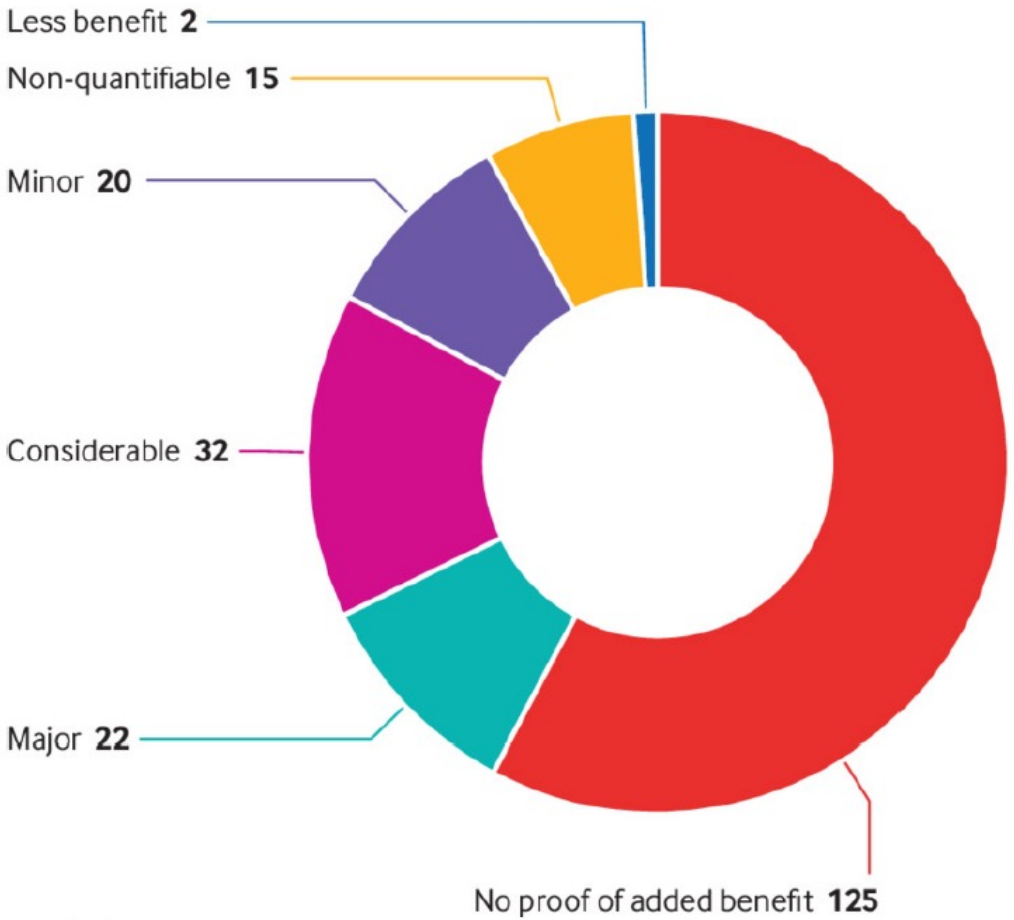


Fig 1 IQWiG's assessment of added benefit of new drugs entering the market in Germany, 2011-17 (Maximum added benefit in any patient group included in a given assessment. Proof requires a statistically significant benefit on patient relevant outcomes in a randomised controlled trial or very large benefit in a non-randomised trial)

IQWIG's assessment 2011-2017

BMJ 2019;366:l4340 doi: 10.1136/bmj.l4340 (Published 10 July 2019)

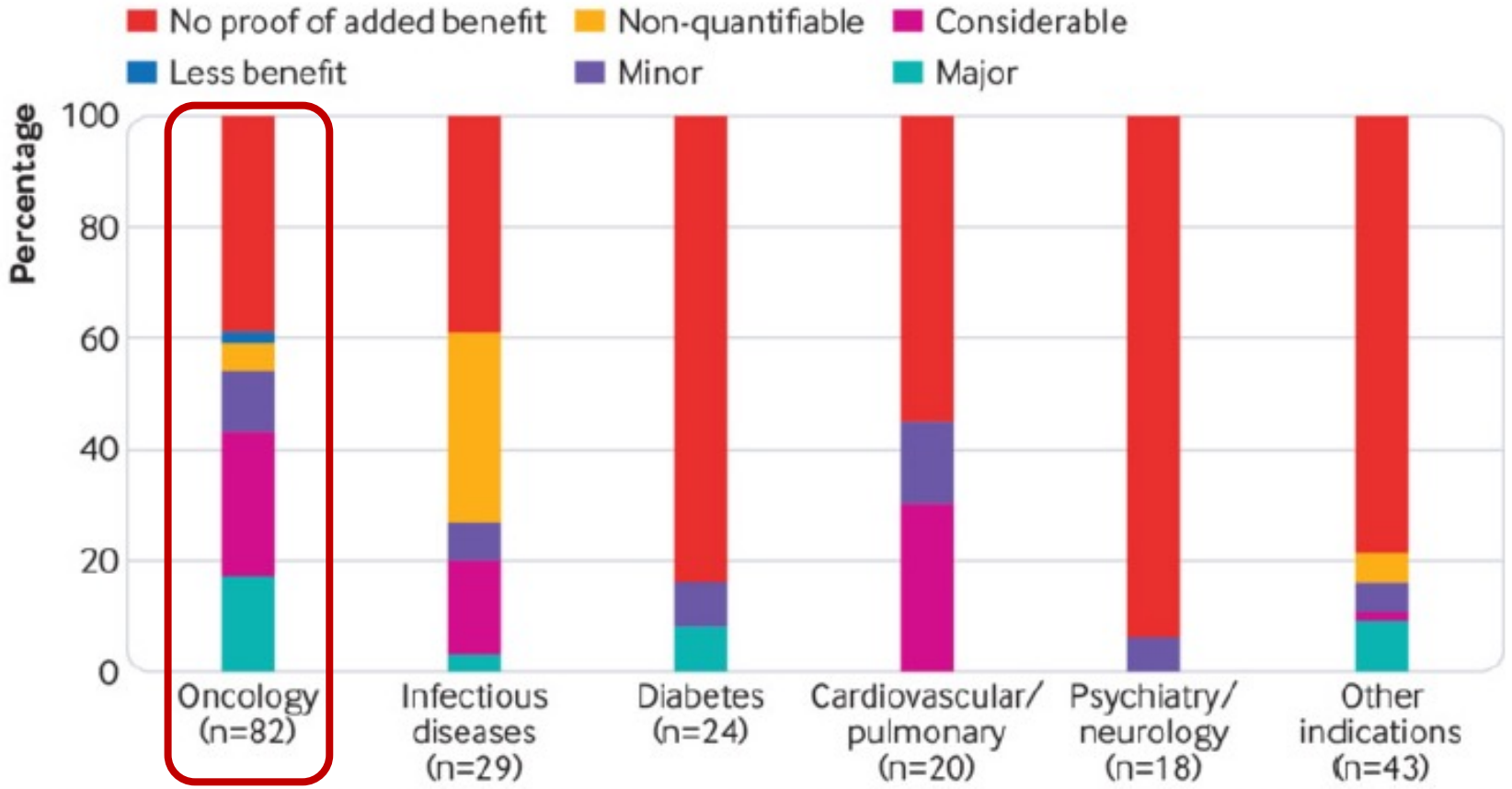


Fig 2 Results of the assessment of added benefit versus standard care by indication for drugs entering the German market, 2011-17

Key messages

- **More than 50% of new drugs lack proof of added therapeutic benefit**
- **To increase innovation: comparative data at the point of drug approval**
- **Reimbursement and pricing at levels that reward relevant outcomes**

➢ **Legal and regulatory framework should be revised :**
Introduce new drug development models/focus on the needs of patients

BMJ 2019;366:l4340 doi: 10.1136/bmj.l4340 (Published 10 July 2019)

Rare disease patient populations are defined in law as:

- **US:** <200,000 patients (<6.37 in 10,000, based on US population of 325m)
- **EU:** <5 in 10,000 (<256,000 patients, based on EU population of 512m)
- **Japan:** <50,000 patients (<4 in 10,000 based on Japan population of 126m)

Financial incentives by law include:

Orphan drug exclusivity

During the period of marketing exclusivity, the regulatory bodies are barred from approving the same product for the same orphan indication. A product holding several separate orphan designations for different indications can have several separate market exclusivities, which can run concurrently.

- **US:** Seven years of marketing exclusivity from approval.
- **EU:** Ten years of marketing exclusivity from approval.
- **Japan:** Ten years registration validity period (also known as re-examination period).

Reduced R&D costs, tax credits, and fees

- **US:** 50% Tax Credit on R&D Cost (owing to new tax legislation, likely to decrease to 25%).
- **US:** R&D Grants for Phase I to Phase III Clinical Trials.
- **US:** User fees waived (FFDCA Section 526: Company WW Revenues <$50m).
- **EU:** EMA protocol assistance at a reduced charge.
- **EU:** Administrative and procedural assistance at a reduced fee for small and medium sized enterprises.
- **EU:** The EMA does not offer research grants but funding is available for the European Commission (EC) and other sources, such as Horizon 2020 and E-Rare.

From blockbuster to “nichebuster”: how a flawed legislation helped create a new profit model for the drug industry

Twenty years ago, the EU passed a law to motivate the drug industry to develop medicines for rare diseases. But a system intended to help patients with neglected maladies primarily turned into a corporate cash machine. **Daan Marselis** and **Lucien Hordijk** report

Table 2 | Nichebuster orphan medicines with a revenue higher than €1bn in 2019.

Product	Revenue 2019 (€)
Revlimid	10 790 457 540
Imbruvica*	7 196 902 261
Soliris	3 512 907 246
Darzalex	2 668 684 351
Pomalyst/Imnovid	2 534 270 963
Jakavi/Jakafit	2 491 426 781
Sprycel	1 878 226 811
Spinraza	1 866 654 798
Tasigna	1 673 342 234
Ofev	1 491 000 000
Xyrem	1 462 101 656
Afinitor/Votubia	1 366 266 133
Symkevi/Symdeko	1 261 944 098
Revolade/Promacta	1 260 347 130
Orkambi	1 185 589 283
Opsumit	1 181 235 535
Glivec	1 124 165 554
Eloctate	1 115 519 700
Lynparza	1 066 405 555
Esbriet	1 013 451 262

* Imbruvica is sold by Johnson & Johnson and AbbVie. †Jakavi/Jakafi is sold by Novartis and Incyte.

Cite this as: *BMJ* 2020;370:m2983
http://dx.doi.org/10.1136/bmj.m2983

Current Perspective on Drugs for Cancer
The Best of Times, the Worst of Times"* –
Cancer Drug Development and Approval, Pricing

This is a time of **unprecedented hope in the development of treatments for cancer.** For many patients, it can also be a time of despair and economic hardship. **New drugs and treatment regimens proliferate faster than most physicians can keep pace with**. Comunication choices among the options in disseminated cancer….. can become almost impossible in a context of **month-by-month change in complex treatment strategies and new subgroup classifications**. And faced with the urgency of this task, the traditional methodology of randomized clinical trials may be seen too slow and cumbersome.

* Lehmann R. & Gross C.P., JAMA Intern. Med. 2019, 179, 913

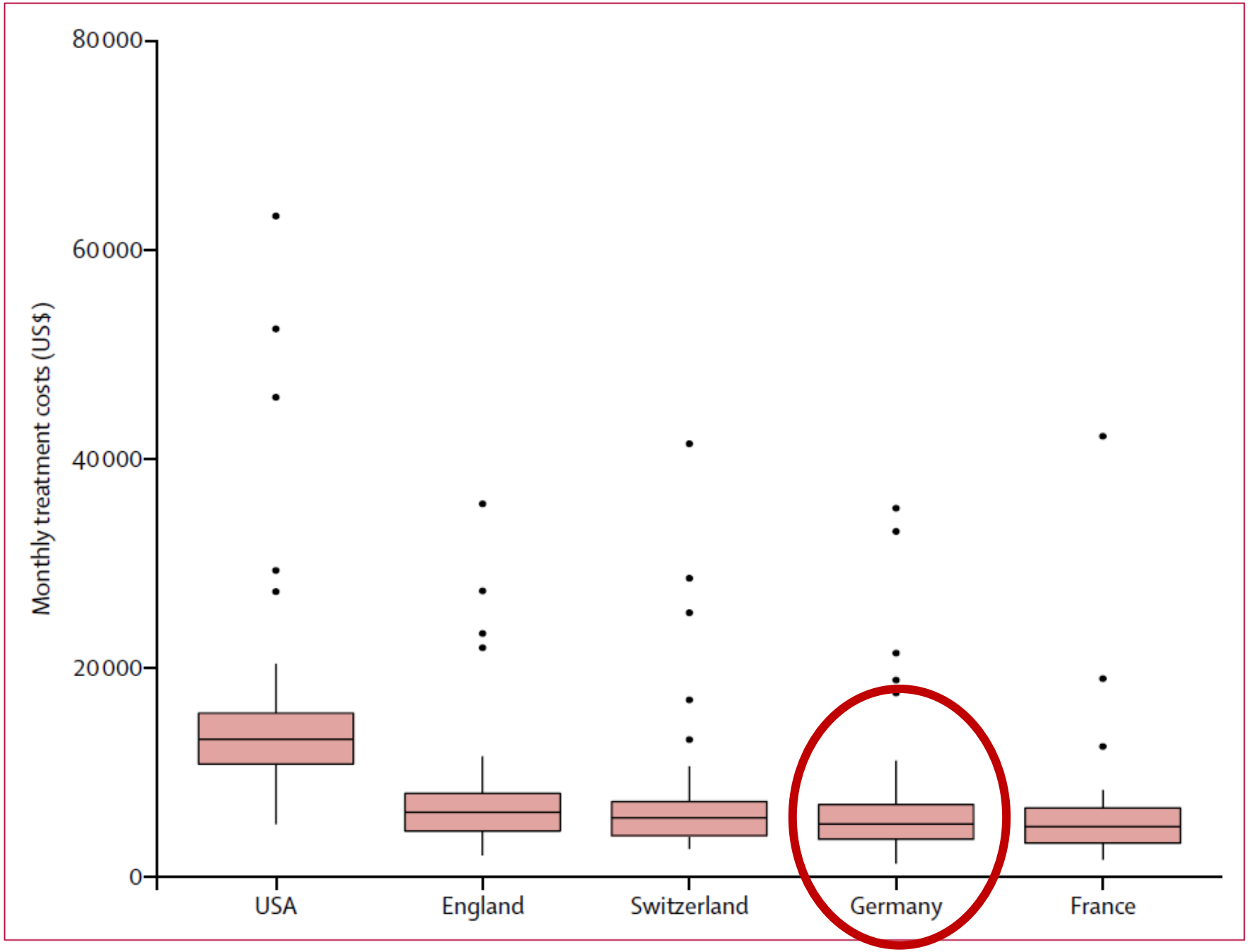
Prices and clinical benefit of cancer drugs in the USA and Europe: a cost–benefit analysis

Kerstin N Vokinger, Thomas J Hwang*, Thomas Grischott, Sophie Reichert, Ariadna Tibau, Thomas Rosemann, Aaron S Kesselheim*

Background Increasing cancer drug prices are a challenge for patients and health systems in the USA and Europe. By contrast with the USA, national authorities in European countries often directly negotiate drug prices with manufacturers. The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) developed frameworks to evaluate the clinical value of cancer therapies: the ASCO-Value Framework (ASCO-VF) and the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). We aimed to assess the association between the clinical benefit of approved cancer drugs based on these frameworks and their drug prices in the USA and four European countries (England, Switzerland, Germany, and France).

Methods For this cost–benefit analysis, we identified all new drugs with initial indications for adult cancers that were approved by the US Food and Drug Administration between Jan 1, 2009, and Dec 31, 2017, and by the European Medicines Agency up until Sept 1, 2019. For drugs indicated for solid tumours, we assessed clinical benefit using ASCO-VF and ESMO-MCBS. We compared monthly drug treatment costs between benefit levels using hierarchical linear regression models, and calculated Spearman's correlation coefficients between costs and benefit levels for individual countries.

Lancet Oncol 2020; 21: 664–70



Lancet Oncol 2020; 21: 664–70

Figure 1: **Monthly treatment costs of approved cancer drugs in the USA and Europe**

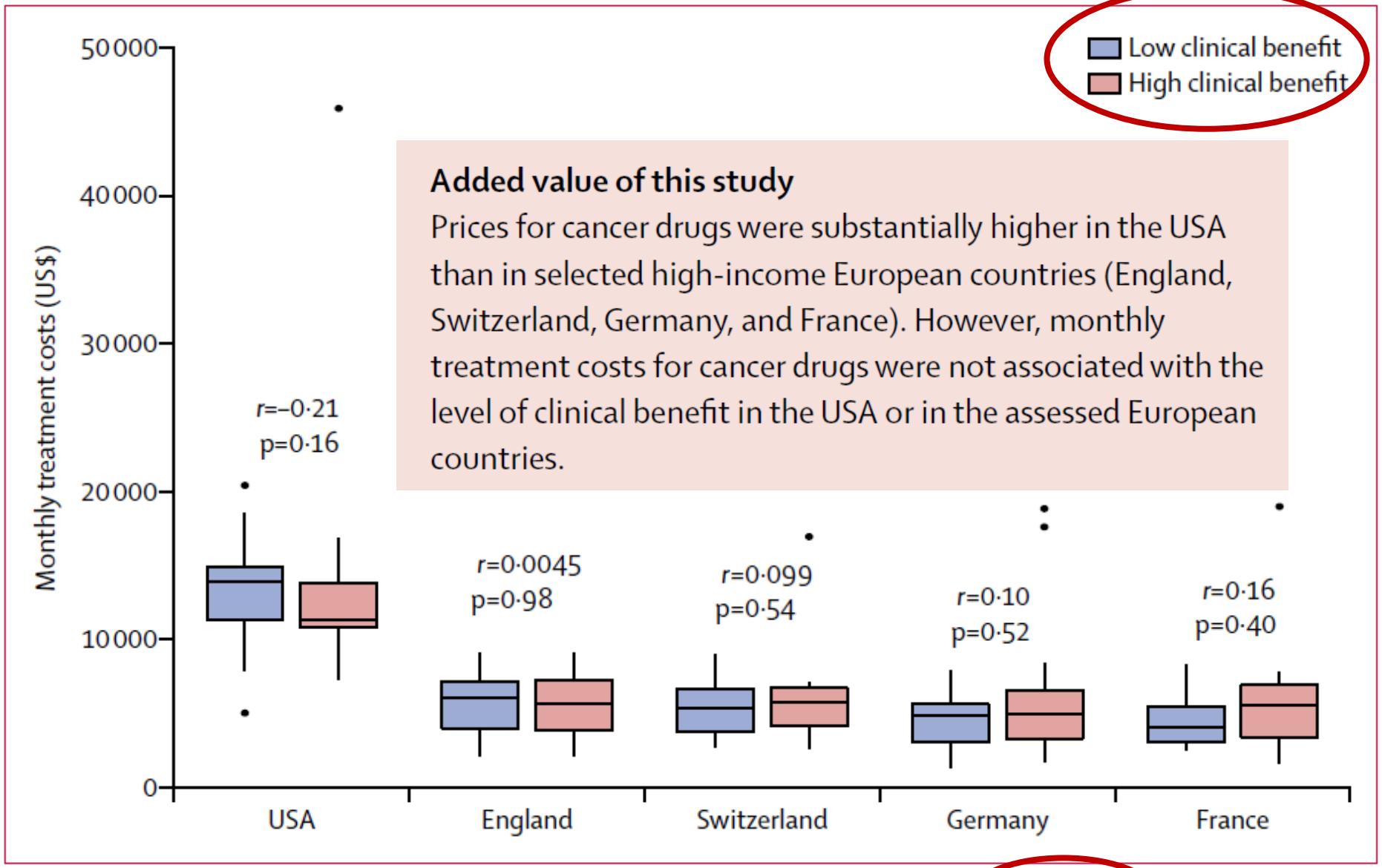


Figure 3: Monthly drug treatment costs stratified by clinical benefit using the ESMO-MCBS

Lancet Oncol 2020; 21: 664–70

JAMA Internal Medicine | Original Investigation

Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval

Vinay Prasad, MD, MPH; Sham Mailankody, MBBS

Key Points

Question What is the estimated research and development spending for developing a cancer drug?

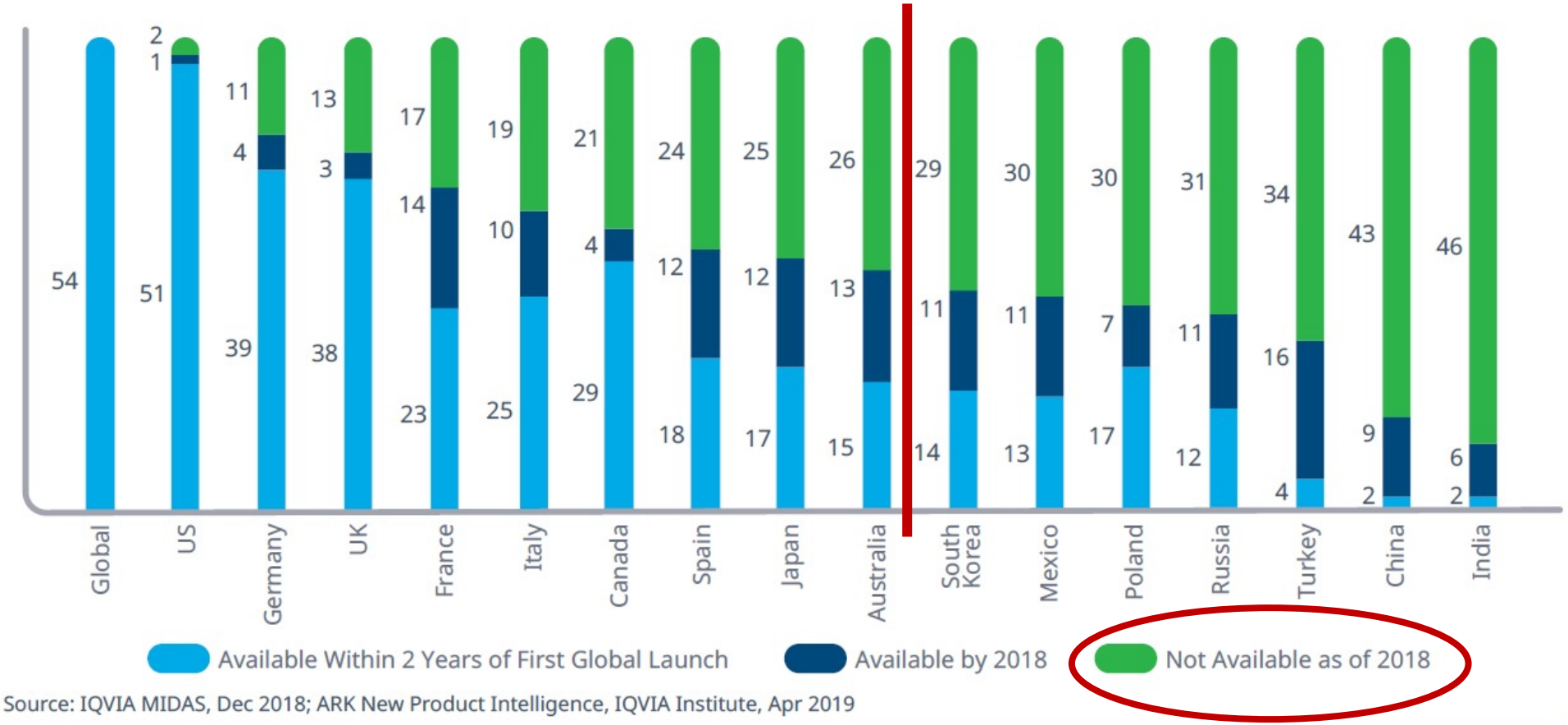
Findings In this analysis of US Securities and Exchange Commission filings for 10 cancer drugs, the median cost of developing a single cancer drug was $648.0 million. The median revenue after approval for such a drug was $1658.4 million.

Meaning These results provide a transparent estimate of research and development spending on cancer drugs and show that the revenue since approval is substantially higher than the preapproval research and development spending.

JAMA Intern Med. doi:10.1001/jamainternmed.2017.3601
Published online September 11, 2017.

Patients in only nine countries have access to more than half of recently launched global cancer medicines

Exhibit 24: Availability in 2018 of Oncology Medicines Launched in 2013–2017



Source: IQVIA MIDAS, Dec 2018; ARK New Product Intelligence, IQVIA Institute, Apr 2019

JAMA | Original Investigation

Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies

Fred D. Ledley, MD; Sarah Shonka McCoy, PhD; Gregory Vaughan, PhD; Ekaterina Galkina Cleary, PhD

Key Points

Question How do the profits of large pharmaceutical companies compare with those of other companies from the S&P 500 Index?

Findings In this cross-sectional study that compared the profits of 35 large pharmaceutical companies with those of 357 large, nonpharmaceutical companies from 2000 to 2018, the median net income (earnings) expressed as a fraction of revenue was significantly greater for pharmaceutical companies compared with nonpharmaceutical companies (13.8% vs 7.7%).

Meaning Large pharmaceutical companies were more profitable than other large companies, although the difference was smaller when controlling for differences in company size, research and development expense, and time trends.

JAMA. 2020;323(9):834-843. doi:10.1001/jama.2020.0442

The JAMA Forum

Rising Prices and Health Care "Empires"

Andrew B. Bindman, MD

Recommendation for further reading

2 Editorials
10 Articles

Are Pharmaceutical Companies Earning Too Much?

David M. Cutler, Ph

JAMA March 3, 2020 Volume 323, Number 9

Some of the most valuable innovations known to medicine have come from the pharmaceutical industry. Yet, the cost of those innovations places new drugs out of reach for many patients and significantly burdens others. Are pharmaceutical companies earning too much? Deciding whether pharmaceutical companies earn too much money is complicated.

Collectively, the articles in the current issues of *JAMA* and *JAMA Internal Medicine*, along with the illustrated cover of *JAMA*, paint a concerning picture about the relationships among rising drug prices, pharmaceutical industry profits, uncertainty about pharmaceutical R&D costs, and lobbying and political donations to gain influence with legislators. We anticipate that publication of this information will further stimulate the ongoing national debate on prescription drugs and help rein in increasing drug prices while sustaining innovation in drug development, which is so critical to the health of individuals both in the US and around the world.

3 Take-home messages

- **EMA and FDA have increasingly accepted less data and more surrogate endpoints, and have shortened their review times.**
- **More than 50% of new drugs lack proof of added therapeutic benefit.**
- **Monthly treatment costs for cancer drugs are not associated with the level of clinical benefit in Europe/USA.**