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ANALYSIS

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

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Medicines regulators around the world are pursuing a strategy aimed at accelerating the development and approval of drugs.[1 2] These approaches are based on the assumption that faster access to new drugs benefits patients. The rhetoric of novelty and innovation creates an assumption that new products are better than existing ones.

But although gaps in the therapeutic armamentarium undoubtedly exist, research covering drug approvals since the 1970s suggests only a limited number of new drugs provide real advances over existing drugs.[3-9] Most studies put the proportion of true innovation at under 15%, with no clear improvement over time.

No evidence of added benefit for most new drugs

By law, the German health technology assessment agency IQWiG (Institute for Quality and Efficiency in Health Care) must investigate the added benefit of new drugs compared with standard care. The classification of added benefit—as minor, considerable, or major—depends on the importance of the outcome and magnitude of the treatment effect, and the information affects pricing and treatment decisions (box 1).

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Box 1: Early assessment of benefit of new drugs in Germany

On 1 January 2011, Germany introduced early benefit assessment (Frühe Nutzenbewertung) of new drugs through the reform of the market for medicinal products act (AMNOG). Its aim is to determine whether a new drug has any added benefit over standard care. The Federal Joint Committee (G-BA), the main decision making body within the German statutory health insurance system, is responsible for the assessment procedure and ultimately decides on the added benefit.

The G-BA specifies the standard care based on criteria laid down in the law. According to these criteria, standard care is an approved and reimbursed intervention that is established in clinical practice and for which a benefit has been proved according to the standards of evidence based medicine (predominantly based on studies with patient relevant outcomes). If appropriate, standard care might also be watchful waiting or best supportive care.

The added benefit of the new drug is primarily determined by a direct or a suitable indirect comparison (only adjusted indirect comparisons using appropriate common comparators are accepted[10]) with standard care using the outcomes of mortality, morbidity (including adverse events), or health related quality of life.

The assessment is performed for the authorised use of both the new drug and standard care. There is a special procedure for orphan drugs with a revenue below €50m (£45m; $57m) a year and these drugs are not included in the current analysis.

Procedure

When a newly approved drug enters the German market, the drug company responsible must submit a standardised dossier containing all available evidence of the drug's added benefit over standard care to the G-BA. The G-BA generally commissions IQWiG to assess the evidence contained in the dossier within three months after market entry. The results of this assessment serve as the basis for G-BA's decisions on the added benefit. After publication of IQWiG's assessment report, the G-BA conducts a commenting procedure and hearing, during which the drug company and other specified parties may submit comments. After evaluation of these comments, the G-BA issues a decision on the probability and extent of added benefit. The final decisions therefore sometimes differ from IQWiG's assessment. For the 216 assessments described in this article, the G-BA's decision was as follows: no added benefit: 115/216 (53%), major added benefit: 1/216 (<1%), considerable added benefit: 55/216 (25%), minor added benefit: 33/216 (15%), non-quantifiable added benefit: 12/216 (6%), less benefit: 0/216 (0%) (https://www.g-ba.de/informationen/nutzenbewertung/).

The conclusions on added benefit are used to inform pricing negotiations between the umbrella organisation of statutory health insurance and the drug company. Even if the G-BA concludes that a new drug has no added benefit, the drug is permitted to stay on the market. However, in general, a new drug with no added benefit should not cost more than standard care. The conclusions on added benefit can also have an important effect on provision of healthcare, as they can also be used for clinical practice guidelines and individual treatment decisions by patients and physicians.

Between 2011 and 2017, IQWiG assessed 216 drugs entering the German market following regulatory approval—152 new molecular entities and 64 drugs granted a new indication. Almost all of these drugs were approved by the European Medicines Agency for use throughout Europe. Thus our results also reflect the outcome of European drug development processes and policies.

Only 54 of the 216 assessed drugs (25%) were judged to have a considerable or major added benefit. In 35 (16%), the added benefit was either minor or could not be quantified. For 125 drugs (58%), the available evidence did not prove an added benefit over standard care for mortality, morbidity, or health related quality of life in the approved patient population (fig 1). Table 1 provides examples of assessment outcomes in the different categories of added benefit. As the effects of drugs often vary between patients, there might be subpopulations benefiting despite no relevant effects in overall study populations. However, IQWiG already considers subgroups by age, sex, disease severity, and further disease specific factors. Of the 89 drugs with an added benefit, 52 (58%) showed an added benefit in the whole approved patient population, and 37 (42%) had an added benefit in only part of the approved patient population.

The situation is particularly egregious in some specialties. For example, in psychiatry/neurology and diabetes, added benefit was shown in just 6% (1/18) and 17% (4/24) of assessments, respectively (fig 2). Presumably, this is because regulators still allow placebo controlled studies even though health technology assessment bodies have long recommended active controlled trials, which provide more useful information.[13-15] Figure 2 also shows that drug development and approval do not cover the various indications equally, with oncology drugs by far the most numerous.

What does this mean for drugs available in Europe? Only two drugs (1%) were shown to provide less benefit than standard care, but for 125 we mostly lack the data to say one way or the other. For 64 of these drugs, no studies were available comparing the new drug with standard care. For another 42 drugs, although studies have compared the drug to an active comparator, the comparator was inappropriate—for example, because of off-label drug use or inappropriate dosing regimens. The remaining 19 drugs were tested against an appropriate comparison (standard care) but did not show an advantage (or clear disadvantage) of the new drug.

Illusion of post-approval evidence

Some people have argued that limited information at the time of regulatory approval (and thus widespread use by patients) is the price to be paid for early access to innovative drugs. This argument suggests that research conducted after market entry will ultimately prove the benefit for patients.[16]

The reality, however, looks quite different. For instance, a systematic evaluation of cancer drugs approved by the EMA between 2009 and 2013 showed that most had been approved with no evidence of clinically meaningful benefit on patient relevant outcomes (survival and quality of life), and several years later the situation had little changed.[17] Perhaps more troubling, a systematic review of new drugs for over 100 indications approved by the US Food and Drug Administration on the basis of limited evidence found that superior efficacy on clinical outcomes was confirmed in less than 10% of cases.[18] A higher but still insufficient rate (20%) was shown in a similar publication on cancer drugs.[19]

Despite their promise, a critical and well known problem with post-marketing studies is they often do not happen. Analyses have found that only about half were completed on time[20] or within five to six years.[21] The situation in Germany is similar: none of the six post-approval studies requested on the basis of the initial health technology assessment that were due for reassessment between 2011 and 2017 were conducted. Globally, regulators do little to sanction non-compliant companies.

Me-too drugs

Although the term "me-too drugs" is heard less frequently today, several new drugs with an added benefit in oncology and infectious diseases have the same mode of action, indicating that a commercially successful drug with a new mode of action is often followed by several similar drugs, not real innovation. For instance, the IQWiG analysis showed that in Germany 12 of 48 successful assessments (25%) in oncology were for PD-1 or PD-L1 inhibitors. The various drugs that showed added benefit in hepatitis C all use one of the three types of direct antiviral action or a combination thereof.

Analyses of drug development pipelines show a similar pattern. An international review of ongoing and planned trials in immuno-oncology identified large numbers of trials investigating drugs aimed at the same targets, including even more PD-1 and PD-L1 inhibitors.[22] These findings not only raise doubts about the efficiency of the drug development process but also about whether the current trial landscape is hampering the productive

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development of new treatment options by enrolling large numbers of patients in trials providing at best me-too drugs, wasting money on redundant developments, and failing to develop new approaches with different mechanisms of action aiming at broader patient populations. The me-too trend has been criticised as the greatest impediment to making serious therapeutic advances.[23]

In addition, it has been shown that the newer genome driven cancer therapies, which form an important part of the drugs showing added benefit in our assessments, provide an added benefit for only a minority of patients with advanced cancer.[24] For the overall patient population, the current output of drug development may thus be resulting in even less progress than our assessments suggest.

Effect on patients and healthcare systems

Clinicians and patients deserve impartial and complete information on what to expect from a certain treatment, including information on the benefit of alternative treatments or no treatment. But given the current information gaps this is not possible. As a consequence, patients' ability to make informed treatment decisions consonant with their preferences might be compromised,[25] and any healthcare system hoping to call itself "patient centred" is falling short of its ethical obligations.[26 27]

The information gaps also harm healthcare systems. High levels of uncertainty about treatment benefit jeopardise quality care and impede decision making, particularly on highly priced drugs in economically strained situations.

A new approach

Since drug development, approval, reimbursement, and pricing are highly regulated, the current state of affairs suggests a policy failure. We need new approaches.

We believe that regulators should become far less tolerant of shortened drug development programmes. Restoring their previous policy, they should demand robust evidence from longer term and sufficiently large phase III randomised controlled trials to prove efficacy and safety, which in parallel could be used to collect data for health technology assessment. Current regulatory laws support this suggestion. In addition, given the influence of regulatory decision making on wider healthcare systems, the specification of regulatory approaches should involve all parties responsible for ensuring appropriate healthcare.

Information gaps could be closed further by a mandatory requirement to conduct active controlled trials—if not for approval, then for better understanding of a drug's benefit in the health technology assessment process and in clinical practice. The current initiative on legislation for health technology assessment in Europe is an opportunity to implement such requirements[28] and could improve the information available on new drugs.

In parallel, reimbursement and pricing decisions should avoid incentivising marginal outcomes for patients[29 30] or outcomes based on highly uncertain evidence, but rather reward the achievement of relevant outcomes. Initial steps for defining relevant outcomes have already been undertaken; both the American and the European societies of oncologists have developed evaluation frameworks to grade the benefit of treatments and distinguish marginal from relevant outcomes.[31 32] These frameworks could be a starting point for the discussion and extended to other indications. Patient involvement in these discussions is essential.[33] The discussion on relevant outcomes should also feed back into the discussion on regulatory decision making.

In the longer term, health policy makers need to take a more proactive approach. Rather than waiting for drug companies to decide what to develop, they could define the health system's needs and implement measures to ensure the development of the treatments required. Initiatives for the development of new antibiotics are first examples of such approaches, including one coordinated by the World Health Organization, in which it identifies priority pathogens, reviews development pipelines, and designs and conducts clinical trials in collaboration with commercial and non-commercial partners.[34] A general review of drug development pipelines on a European level taking account of current and expected burden of disease would be a first step to enable policy makers to react to research gaps and realign drug development with public health needs.

Furthermore, new models of drug development might represent an important part of the solution. Triggered by gaps in the development of drugs for neglected diseases or by pressures on the sustainability of healthcare systems, these models are already under discussion or have even been implemented.[35-37] The drug development model of the Drugs for Neglected Diseases initiative (DNDi) is based on needs driven, disease-specific target product profiles. The model also ensures access to new treatments and to knowledge. It is built on the financial and scientific independence of DNDi and on collaboration between public and private partners.[35] A project conducted by the Belgian and Dutch health technology assessment agencies on possible future scenarios for drug development has suggested needs oriented public-private partnerships and not-for-profit drug development as well as new models for the pharmaceutical industry such as "pay for patents" or drug development as a public enterprise.[36]

Another suggestion to improve the efficiency, quality, and relevance of drug development is to use an open source model.[37] The potential advantages of access to the evidence from a whole therapeutic area, which would be part of an open source model, have recently been shown in a project on Alzheimer's disease that has been restricted to regulators but could be expanded to other parties.[38]

Targeted healthcare policy informed by evidence

The setting of healthcare policy goals is highly politicised. Nevertheless, drug policy should be based on specific public health goals. New approaches should be developed based on the evidence describing the performance of current policy frameworks. The outcomes of policy changes should be compared with the public health goals and adjustments made, if necessary.

In conclusion, the outcome of the current drug development processes and policies in Europe is insufficient. Combined action at EU and national levels is required to define public health goals and to revise the legal and regulatory framework, including introducing new drug development models, to meet these goals and focus on what should be the main priority in healthcare: the needs of patients.

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Key messages

- More than half of new drugs in Germany lack proof of added benefit over existing treatments
- To increase innovation manufacturers should be required to submit comparative data at the point of drug approval
- Payers could then set reimbursement and pricing at levels that reward relevant outcomes for patients
- Combined action at EU and national levels is required to revise the legal and regulatory framework, introduce new drug development models, and focus on the needs of patients

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Table

Table 1| Examples of IQWiG assessments of patient relevant outcomes for the different categories of added benefit*

Project ID†	Indication	Test drug versus comparator	Positive effects (hazard or relative risk ratio, 95% CI)	Negative effects‡ (hazard or relative risk ratio, 95% CI)
Major added benefit				
A16-04/A16-34	Mantle cell lymphoma (relapsed or refractory)	Ibrutinib *v* temsirolimus	HRQoL (FACT-G): median time to deterioration 15 *v* 6 weeks (HR 0.53, 0.39 to 0.74)	No significant effects
			HRQoL (FACT-LymS): median time to deterioration 81 *v* 8 weeks (HR 0.30, 0.20 to 0.43)	
			Health status (EQ-5D VAS): median time to deterioration 48 *v* 9 weeks (HR 0.47, 0.33 to 0.68)	
			Serious adverse events: median time to event 61 *v*s 18 weeks (HR 0.53, 0.38 to 0.74)	
			Severe adverse events: median time to event 48 *v* 3 weeks (HR 0.28, 0.20 to 0.39)	
A17-60/A18-24	Plaque psoriasis (moderate to severe, second line)	Guselkumab *v* adalimumab	Remission (PASI 100): 45% *v* 26% (RR 1.70, 1.37 to 2.11)	No significant effects
			Symptoms (PSSD): symptom score 0: 28% *v* 17% (RR 1.73, 1.31 to 2.31)	
			Sign score 0: 24% *v* 10% (RR 2.31 [1.61 to 3.31)	
			HRQoL (DLQI) proportion of patients with DLQI 0 or 1: 57% *v* 39% (RR 1.47, 1.25 to 1.72)	
Considerable added benefit				
A17-40/A18-03	Multiple myeloma (second line)	Daratumumab+bortezomib or lenalidomide *v* bortezomib or lenalidomide	Overall mortality: median time to death NR *v* NR (HR 0.63, 0.47 to 0.84)	Severe adverse events: median time to event 5 *v* 12 weeks (HR 1.40, 1.22 to 1.62)
				Non-serious adverse events: respiratory, thoracic and mediastinal disorders (HR 2.01, 1.67 to 2.42); gastrointestinal disorders (HR 1.50, 1.28 to 1.76)
A11-02	Non-ST elevation acute coronary syndrome	Ticagrelor+ASA *v* clopidogrel+ASA	Overall mortality 3.8% *v* 5.3% (HR 0.73, 0.60 to 0.89)	Non-serious adverse events: dyspnoea 14% *v* 8%; (RR 0.55, 0.49 to 0.62)
			Myocardial infarction 5.9% *v* 7.0% (HR 0.85, 0.72 to 1.00)	Discontinuation due to adverse events 8.2% *v*. 5.7% (RR 0.70, 0.60 to 0.81)
Minor added benefit				
A16-63	Renal cell carcinoma (advanced, second line)	Lenvatinib *v* everolimus	Overall mortality: median time to death 26 *v* 15 months (HR 0.59, 0.36 to 0.97)	Severe adverse events: diarrhoea median time to event NR *v* NR (HR 9.22, 1.18 to 72.19)
A11-30	Elective hip replacement surgery	Apixaban *v* enoxaparin	Symptomatic deep vein thrombosis 0.14% *v* 0.38% (Peto odds ratio 0.40, 0.17 to 0.93)	No significant effects
No proof of added benefit				
A16-67	Pulmonary arterial hypertension	Macitentan *v* physician's choice	No relevant studies: only placebo controlled studies available	
A17-18/A17-43	Rheumatoid arthritis	Tofacitinib+ methotrexate *v* adalimumab+ methotrexate	No significant effects	No significant effects
A13-38	Multiple sclerosis	Teriflunomide *v*. interferon beta-1a	Injection site reactions 0 % *v* 21.8 % (Peto odds ratio 0.10, 0.04 to 0.24)	Alopecia 20.0% *v* 1.0 % (Peto OR 7.01, 2.95 to 16.65)
			Flu-like symptoms 2.7 % *v* 53.5% (RR 0.05, 0.02 to 0.16)	Diarrhoea 20.9% *v* 7.9%; (RR 2.64, 1.24 to 5.63)
Less benefit				
A15-31	Chronic obstructive pulmonary disease (GOLD 3 or 4)	Tiotropium+olodaterol *v* tiotropium	No significant effects	Severe exacerbations 18% *v* 4% (RR 3.32, 1.02 to 10.84)

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Table 1 (continued)

Project ID†	Indication	Test drug versus comparator	Positive effects (hazard or relative risk ratio, 95% CI)	Negative effects‡ (hazard or relative risk ratio, 95% CI)
A17-27	Melanoma (advanced, first line)	Nivolumab+ipilimumab *v* nivolumab	No significant effects	Symptoms (EORTC QLQ-C30) diarrhoea (MD 5.3, 3.2 to 7.5; Hedges' g 0.52, 0.31 to 0.74)
				Serious adverse events: median time to event 2 *v* 22 months (HR 2.93, 2.24 to 3.82)
				Severe adverse events: median time to event 2 *v* 11 months (HR 2.36, 1.86 to 2.99)
				Discontinuation because of adverse events 44% *v* 14% (RR: 3.25, 2.24 to 4.71)

* Overall conclusion on added benefit is based on the weighing of positive and negative effects. All example assessments are based on randomised controlled trials, which are the preferred study type. Within the 216 assessments, there were three cases in which an added benefit was not derived from randomised trial data: two assessments of ledipasvir-sofosbuvir and one assessment of sofosbuvir. Details of the methods used to determine added benefit are published elsewhere.[10 11]

† Full project reports are available online.[12]

‡ Severe adverse events are those classified as CTCAE grade 3/4 (Common Terminology Criteria for Adverse Events)

ASA: acetylsalicylic acid. DLQI: Dermatology Life Quality Index. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. EQ-5D: European Quality of Life-5 Dimensions. FACT-G: Functional Assessment of Cancer Therapy-General. FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale. GOLD: Global Initiative for Chronic Obstructive Lung Disease. HR: hazard ratio. HRQoL: health related quality of life. MD=mean difference. NR: not reached. PASI: Psoriasis Area Severity Index. PSSD: Psoriasis Symptom and Sign Diary.

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Figures

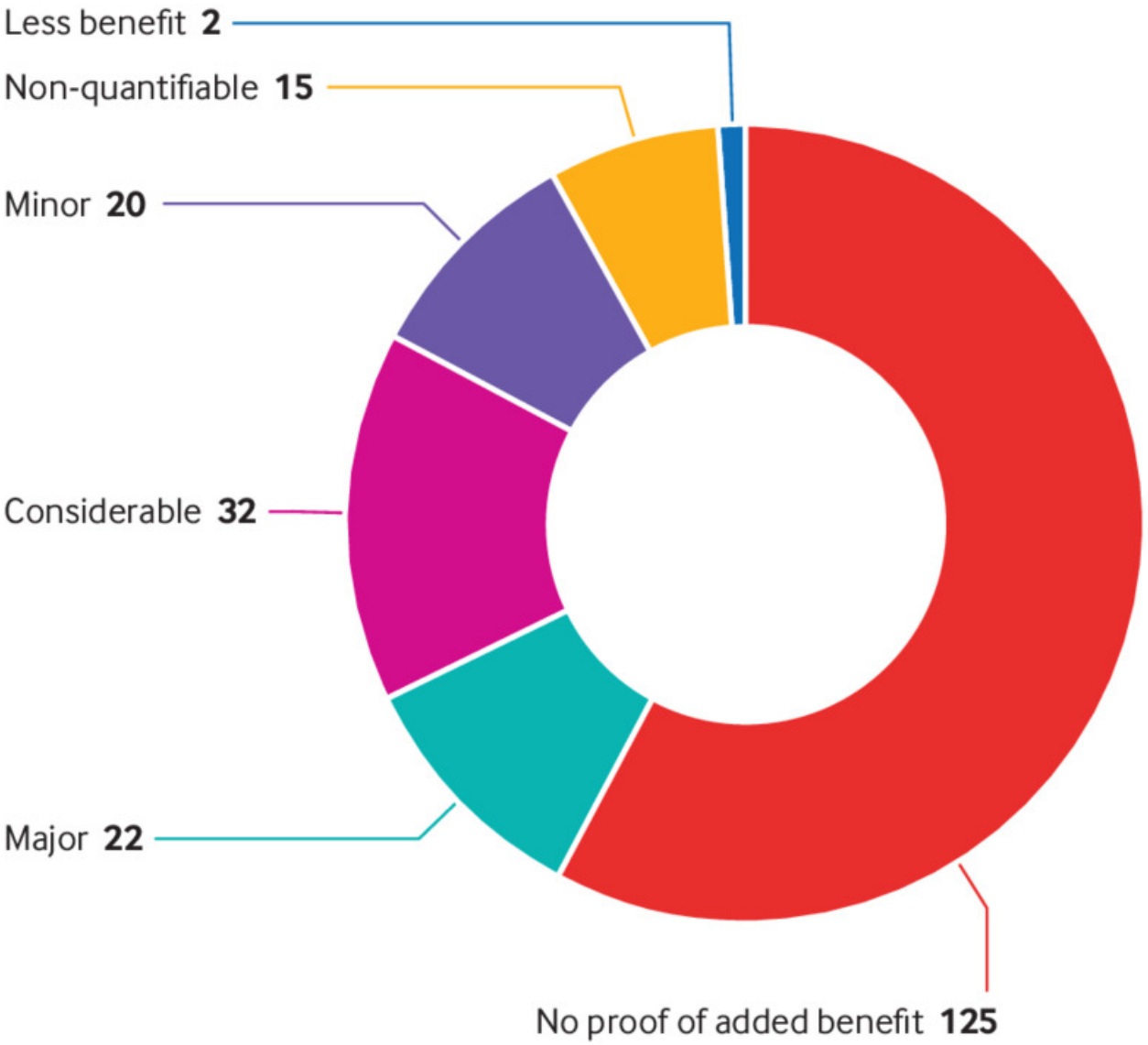

Fig 1 IQWiG's assessment of added benefit of new drugs entering the market in Germany, 2011-17 (Maximum added benefit in any patient group included in a given assessment. Proof requires a statistically significant benefit on patient relevant outcomes in a randomised controlled trial or very large benefit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

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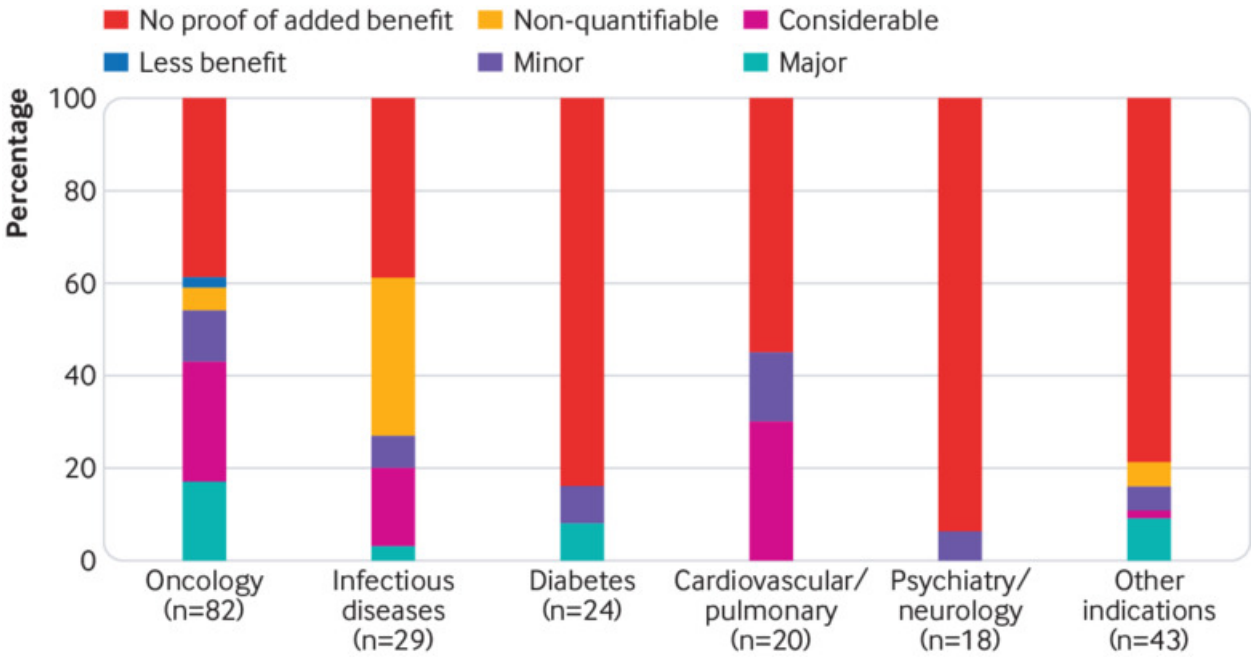

Fig 2 Results of the assessment of added benefit versus standard care by indication for drugs entering the German market, 2011-17

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