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Physician information via software: Orientation or control?

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Goals of the plattform

In 2011, the legislator initiated a paradigm shift in the field of pharmaceutical supply in Germany, with far-reaching consequences. The principle, based on the AMNOG, provides that: for new active substances brought on the German market, the pharmaceutical company must prove an additional patient-relevant benefit as compared to the available standard of treatment – i.e. the appropriate comparative treatment (ACT) – if a higher reimbursement price is sought than for the ACT. The additional benefit is evaluated and determined by the Federal Joint Committee (G-BA), generally on the basis of proposals from the IQWiG. Pricing mainly depends on the result of this additional benefit assessment.

The assessment of the additional benefit by the G-BA is the result of expert work based on a law and procedural and methodical regulations (e.g. IQWiG methods). The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds (MDK, Medizinischer Dienst der Krankenkassen) and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new pharmaceuticals, likewise classified and interest-based, are submitted to the G-BA by the pharmaceutical companies, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on Benefit Assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

- Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,
- Working towards international standards of evidence-based medicine and of health economy being adhered to and applied,
- Determining whether and to what extent actual patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life are identified and which methodological problems occur during the process,
- Identifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure.

The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. According to the Advisory Council, a dialogue about the results of the assessment and the applied benefit assessment methods is essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new pharmaceuticals for patients earlier than it was previously the case.

The Interdisciplinary Platform is a result of the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include AbbVie Deutschland GmbH & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Association of Research-Based Pharmaceutical Companies (vfa, Verband Forschender Arzneimittelhersteller e.V.), and Xcenda GmbH.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Health benefits and harms: AMNOG addresses an old question in a new form

By Professor Jörg Ruof

„I will follow that system of regimen which, according to my ability and judgement, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous."

Although the origin of this wording from The Oath by Hippocrates dates back more than 2,000 years, it is virtually unparalleled in terms of topicality.

This means that the two formative and polar terms of every AMNOG procedure have already been defined in ancient Greek medicine. Thus, the medical task and art is to guide „the sick" between the two poles of „benefit" and „harm" to the best of one's ability. Even in the age of a highly-specialised, precision-oriented and increasingly digitised medical world, these basic principles remain unchanged. At the same time, it is undisputed that „the sick" will feel better with increasing competence and precise judgement of the responsible physicians.

Findings from AMNOG procedures represent an enormous fund of scientific information to enhance both decision-making and therapy competency in daily medical practice. The frequently cited precious social asset of „medical therapeutic freedom" requires continuous training and updating of knowledge to ensure effective treatment of patients. In daily practice, there is controversy about whether this evidence shall not only serve as a tool for information of physicians, but also for prescription control.

In the British health care system, this development was pushed forward to new extremes. Accordingly, the National Institute for Health and Clinical Excellence was renamed National Institute for Health and Care Excellence reflecting the far-reaching claim of NICE-Chairman David Haslam to actively participate in the development of treatment guidelines in healthcare. However, it remains to be seen whether the conceptual foundations of NICE, like cost effectiveness which is often given priority in reimbursement decisions, are suitable to promote optimisation of care in accordance with patient's well-being.

Thus, the design of the German Physician Information

System (PIS) and – in light of the decision by the Berlin-Brandenburg Superior State Social Court – controversial handling of mixed prices, were the conference topic of the 7th Interdisciplinary Platform on Benefit Assessment. We are pleased that we were able to recruit various experts of the healthcare sector to outline their positions:

- In their articles, Dr Steiner and Professor Wörmann explain the physicians´ perspective. Dr Steiner considers the PIS as an important instrument to support the selection of the appropriate therapy and should not be used for prescription control. Professor Wörmann focuses on the relevance of therapy algorithms for the medical treatment decision. Using the example of prostate cancer, he illustrates the dynamics of the underlying treatment algorithms and necessity of continuous adjustment of the therapeutic approach.
- Mr Kaesbach evaluates mixed pricing and subgrouping from the Statutory Health Insurance Funds' (GKV) perspective. He answers the title question as to whether subgrouping and mixed pricing are stipulated in the AMNOG process with a clear „Yes". This results in a conflict with the efficiency principle on which coverage of the GKV is based in accordance with a careful economic use. He indicates the importance of this issue for the forthcoming proceedings before the Federal Social Court of Germany (BSG).
- The team of the University of Bielefeld presents an empiric analysis on mixed prices. Professor Greiner and Mr Witte discuss both potential alternatives and further development options for the mixed price concept.
- Professor Wasem introduces the terms of a „small" and „large mixed price" and their differentiation. Ten theses are formulated from a health-economic view and based on the broad range of experience of the arbitration board that should be taken into consideration in the assessment and processing of the Superior State Social Court (LSG) decision.
- Mrs Fischer makes a plea for maintaining and optimising the mixed price. She outlines the position of the pharmaceutical industry that the mixed price itself is not the problem, but the solution of the underlying problem.

It remains to be seen whether the Ministry will be able to reconcile these partly widely separated positions with the design of the regulation on the PIS. A heartfelt thank you to all participants and speakers/authors of the Interdisciplinary Platform for an enthusiastic exchange, to our colleagues of the Advisory Council for their content-related support of both conference and report as well as to our sponsors – without their support the platform would not exist.

A very special word of thanks goes to Dr Bausch who is somehow the founding father and tireless engine of this initiative and has managed and influenced the platform together with Dr Aidelsburger over the last years with great entrepreneurial foresight and profound knowledge of the German health care sector. He handed over his position to me at the last conference.

And finally, I would like to take this opportunity to draw your attention to the next conference and report on the topic „European HTA assessment".

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Current state of PIS preparation from statutory health insurance physicians' perspective

Dr Sibylle Steiner | Department head of the National Association of Statutory Health Insurance Physicians (KBV)

Discussions about the introduction of the Physician Information System (PIS) for the representation of the decisions of the Federal Joint Committee (G-BA) in the practice software of physicians continue. Earlier this year, German physicians issued a joint statement. They see the PIS generally as a support tool for the physician in the selection of a suitable pharmaceutical within the scope of their therapy decision. According to their opinion, it must not be abused as an instrument for prescription control. Moreover, the National Association of Statutory Health Insurance Physicians (KBV) has a clear vision of the design of the PIS. Statutory health insurance physicians were extremely worried by the decision of the Berlin-Brandenburg Superior State Social Court on mixed pricing. According to their opinion, physicians in the statutory health insurance system might act uneconomically, if they prescribe a pharmaceutical for patient groups without an additional benefit, provided the mixed price would drive up therapy costs as compared to the appropriate comparative treatment (ACT). Alternative approaches are required to make an economic prescription of a new pharmaceutical possible over the whole field of application that has been divided by the G-BA into several subgroups with and without additional benefit.

The main goal of the additional benefit assessment by the G-BA is to establish a fair price for the new pharmaceutical that is launched onto the German market. Moreover, physicians should be better informed about G-BA decisions on these new pharmaceuticals to ensure that they will actually be prescribed on a timely basis. For this purpose, G-BA benefit assessment decisions should be integrated into the physicians' practice software. To establish a Physician Information System (PIS) as an instrument, the Federal Ministry of Health will issue a regulation.

Position of German physicians

Their position on the goal and purpose of the PIS was summarised by the National Association of Statutory Health Insurance Physicians (KBV), German Medical Association (BÄK), Drug Commission of the German Medical Association (AkdÄ), German Hospital Federation (DKG), Association of the Scientific Medical Societies in Germany (AWMF), and Association of Statutory Health Insurance Physicians Westphalia-Lippe in a common statement. This statement is also supported and promoted by the BAG Patient Support Group (BAG Selbsthilfe) (see box).

Current state of PIS preparation and further considerations

It is not only about the aim of the PIS, but also about the specific question as to how the information shall be provided in the prescription software. A detailed proposal was provided in Volume 6 of February 2018[1]. In summary, the following requirements should be taken into account during the implementation of the PIS to create added value for physicians in the statutory health insurance system: Pharmaceuticals for which an early benefit assessment was performed must be clearly marked as such in the prescrip-

Common statement on the Physician Information System (PIS)

The Act on Strengthening Pharmaceutical Supply in Statutory Health Insurance (AMVSG) requires that the results of the early benefit assessment are used faster and more extensively for the benefit of patient care. For this purpose, the results of the early benefit assessment must be provided to physicians in a readily understandable form. A Physician Information System (PIS) shall be established as an instrument for this purpose. The required regulation will be issued by the Federal Ministry of Health.

German physicians generally consider such a PIS as a support tool for the selection of a pharmaceutical within the scope of treatment decision. However, the PIS must not be abused as an instrument for prescription control. „Information" must not turn into „prescription control by health insurance funds" that might lead to prescription restrictions and increased recourse risk for physicians.

During the AMNOG procedure, the Federal Joint Committee (G-BA) evaluates the additional benefit of recently launched pharmaceuticals against the appropriate comparative treatment (ACT). The proof of the extent of the additional benefit serves as evaluation criterion which in turn serves as a basis for subsequent price negotiations between the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and pharmaceutical company. Thus, health insurance funds are responsible for an economic pricing for a new pharmaceutical across the field of application.

However, the results of the early benefit assessment of the G-BA cannot be transferred into the PIS 1:1. Early benefit assessment is generally based on one and rarely on several clinical studies with selected study populations that are not common in daily clinical practice. Moreover, in approximately half of the new pharmaceuticals the field of application is divided into several patient groups. During early benefit assessment, these subgroups are not always the same for the same indications. If there are no studies for certain patient groups against the appropriate comparative treatment, an additional benefit is considered not proven for the G-BA. However, this cannot a priori be equated with a lack of benefit.

For example, in case of an intolerance or failure of the treatment standard, patients need alternatives to an approved active substance, even if an additional benefit has not or not yet been proven for one or another subgroup. Prescription of a certain pharmaceutical must not be regarded as an uneconomic behaviour in these cases. In this context, discussions are underway as to whether physicians shall document subgroup and thus additional benefit category of the patient on the prescription. Physicians must be concerned that a prescription in a patient group without an additional benefit will be evaluated immediately by health insurance funds and considered uneconomic.

The PIS must provide support to the physician. A co-designing role of the pharmaceutical company is refused. This is the only way to ensure that the PIS represents independent information supporting an evidence-based medical therapy decision. Representation in the PIS must neither support nor promote any change of medication if this is not required to avoid poor treatment outcomes and therapy adherence.

The PIS must be both well understandable and diagnostically conclusive enabling optimisation of patient care. It must not be used for prescription control procedures.

Implementation of the regulation must not lead to an increased documentation effort and level of bureaucracy. The costs for the development, use, maintenance, and further development of the PIS must be fully borne by health insurance funds.

tion software. Details about a certain pharmaceutical should be provided via the prescription software based on the indication and all decisions should be summarised for one indication. For this purpose, a table with a summary of all G-BA decisions seems to be the best option with all results of patient-relevant endpoints of the studies used for benefit assessment by mortality, morbidity, safety, and quality of life. In this context, the appropriate comparative treatment that was used for comparison should also be mentioned.

Moreover, additional levels of information depth should be available, in order to provide information on the requirements for a quality-secured application and G-BA decision documents, as well as notes on any circumstances in which prescription might be an exempt from efficiency audits. Further considerations include that entry to the PIS should generally be via the selected pharmaceutical. This means that upon selection of a pharmaceutical for a patient with a certain disease, the physician will be informed that the selected pharmaceutical underwent an early benefit assessment.

In addition, he could receive a note that other pharmaceuticals that have also been evaluated are available for this indication (based on ICD-10). However, linking several pharmaceuticals at subgroup level is neither reasonable nor practicable, as they are not comparable on subgroup level.

Thus, the current state of the information and – in case of G-BA decisions with a limited duration – the validity period should be highlighted. Last but not least, the PIS information should not only be available in the practice software of statutory health insurance physicians, but also in hospital information systems. As the implementation of these new legal provisions will result in additional expenses and costs for physicians, respectively, appropriate funding schemes are required.

Dr Sibylle Steiner *studied human medicine in Regensburg and Munich from 1987 to 1993 and received the license to practice medicine in 1995. She graduated at the Ludwig Maximilian University (LMU) in Munich and completed her education in Boston, USA with her Masters of Business Administration with focus on Healthcare Management. At the KBV, she was head of the Department Pharmaceuticals from 2008 to 2013 and became Department head of the division Medical and Ordered Services in June 2013.*

The challenge of mixed prices

One main concern of physicians regarding the PIS design is that it might lead to prescription restrictions and an increased recourse risk and might thus restrict their therapeutic freedom. It was expected that upon introduction of the early benefit assessment with the German Pharmaceutical Market Reorganisation Act (AMNOG), responsibility would be transferred from the physicians to health insurance funds and pharmaceutical companies due to agreement or stipulation, respectively, of reimbursement amounts based on G-BA decisions. The fact that physicians were no longer able to assume responsibility for the prices of pharmaceuticals already became apparent with the introduction of rebate agreements especially in the generic segment.

However, positions of all involved parties were controversial from the beginning as to whether and to what extent the early benefit assessment including agreement or stipulation of a reimbursement amount, respectively, allows for economic prescription of a new pharmaceutical over the whole field of application which has been divided by the G-BA into several subgroups with and without additional benefit (see Figure 1).

If the price, i.e. the reimbursement amount, for these new pharmaceuticals was determined on the basis of a mixed price, it will be „too low" in patient groups with a proven benefit and „too high" in patient groups without a proven benefit, respectively, as compared to the appropriate comparative treatment. This may lead to distortions, i.e. the assumed prescription shares for the respective patient groups are not reflected by actual prescriptions. There are many reasons for such a deviation, i.e. prescribing physicians can be responsible for it or epidemiological data might be unclear or insufficient so that the size of the subgroups cannot be clearly defined. Another reason might be that the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and pharmaceutical company use a different subgroup distribution as compared to the G-BA or the arbitration board defines a different distribution on the basis of the expected prescription behaviour. Thus, the latter was the case in the legal dispute about the determination of the mixed price for albiglutide[2].

The fact that according to the Berlin-Brandenburg Superior State Social Court's opinion, physicians in the statutory health insurance system might act uneconomically, if they prescribe a pharmaceutical for patient groups without an additional benefit, provided the mixed price would drive up therapy costs as compared to the appropriate comparative treatment might lead to consequences for prescribing statutory health insurance physicians. Statutory health insurance physicians were extremely concerned by this decision. Upon request, the KBV confirmed that there have been several requests for review and efficiency audits by health insurance funds for prescriptions of pharmaceuticals in subgroups without additional benefit for the indications hepatitis C and multiple sclerosis .

Moreover, in discussions with statutory health insurance physicians and Associations of Statutory Health Insurance Physicians, health insurance funds pointed out that they consider prescriptions in subgroups without additional benefit uneconomic and might evaluate efficiency of such prescriptions in future. Even if there were only few requests for review so far, the potential threat of recourse is a real problem for statutory health insurance physicians.

Therefore, a solution is required that primarily ensures prescription security for statutory health insurance physicians as well as the required planning security for health insurance funds and pharmaceutical companies. This could only be achieved with price-volume agreements and the risk of additional expenditure exceeding the agreements would be borne by the pharmaceutical company. However, if this concept shall not be binding, new feasible approaches must be discussed. As mentioned above, the question of efficiency of the reimbursement amount for pharmaceuticals for which the field of application is divided into various subgroups depends upon a valid assumption of the actual distribution of the patient groups in the daily prescription routine.

There are many reasons against the collection of data from all prescribing physicians. Physicians oppose such a collection, especially against the background of increased bureaucracy, lack of feasibility, high funding requirements, and increased risk of recourse. The possibility to collect data in a panel could be further discussed under the key requisites of clarification with regard to the resulting econo-

Wirtschaftlichkeit von neuen Arzneimitteln

Unklare Verordnungssituation für Vertragsärzte

Phasen	ohne Zusatznutzen	mit Zusatznutzen im gesamten Anwendungsgebiet	mit Zusatznutzen bei Patientengruppen
Markteintritt bis G-BA-Beschluss (Monate 1-6)	Beschluss des G-BA liegt zu diesem Zeitpunkt noch nicht vor. Verordnung kann unwirtschaftlich sein, allerdings erhöhte Beweis- und Darlegungslast durch die Prüfungsstellen!		
G-BA-Beschluss bis Erstattungsbetrag (Monate 6-12)	**i.d.R. unwirtschaftlich**	**unklar**	Patientengruppen **ohne** Zusatznutzen: **i.d.R. unwirtschaftlich** Patientengruppen **mit** Zusatznutzen: **unklar**
Erstattungsbetrag (ab Monat 13)	**Wirtschaftlichkeit** hergestellt über **Erstattungsbetrag**	eher **wirtschaftlich**	Patientengruppen **ohne** Zusatznutzen: Position GKV: i.d.R. **unwirtschaftlich,** sofern teurer als zVT Patientengruppen **mit** Zusatznutzen: eher **wirtschaftlich**

Quelle: KBV – eigene Darstellung

Abbildung 1: Ärzte fürchten, dass die Regressbedrohung angesichts des Streits um Mischpreise noch zunehmen könnte.

mic prescription of pharmaceuticals with mixed prices as well as adequate financing of panel survey. Successful examples for such a panel survey include Sentinel by the Robert Koch Institute or Zi-Praxis-Panel by the Central Research Institute of Ambulatory Health Care.

References:

[1] Steiner, S. (2018). How can the information create added value for physicians? Interdisciplinary Platform on Benefit Assessment– Physician information via Software: Ways and goals. Volume 6, February 2018, ISSN 2364-916X, Springer Medizin.

[2] Berlin-Brandenburg Superior State Social Court. Ref.: L9 KR 213/16 KL, decision dated 28 June 2017.

What information do physicians need for therapy decisions?

Professor Bernhard Wörmann | German Society for Haematology and Oncology, Division of Haematology, Oncology, and Tumour Immunology at the Charité Universitätsmedizin Berlin

Therapy decisions are generally embedded in several complex, incremental algorithms. They are based on predictive diagnostics and current state of knowledge in consideration of the patient's individual comorbidity. In the field of oncology, there are several equal therapy options for an increasing number of cases. In very dynamic specialist fields, algorithms must be updated at short intervals. Determinations on the efficiency of a certain pharmaceutical are one important, but only one part of the therapy decisions in the field of oncology.

Introduction

Every therapy decision stands at the end of a chain of collected and evaluated information about the respective disease and the patient as a whole person. Kind and scope of the required information are defined by the disease itself, the therapy options, and the therapeutic goals set by the patient.

Using the example of malignant diseases, the systematic approach and handling of fast developing standards in diagnostics and therapy can be demonstrated.

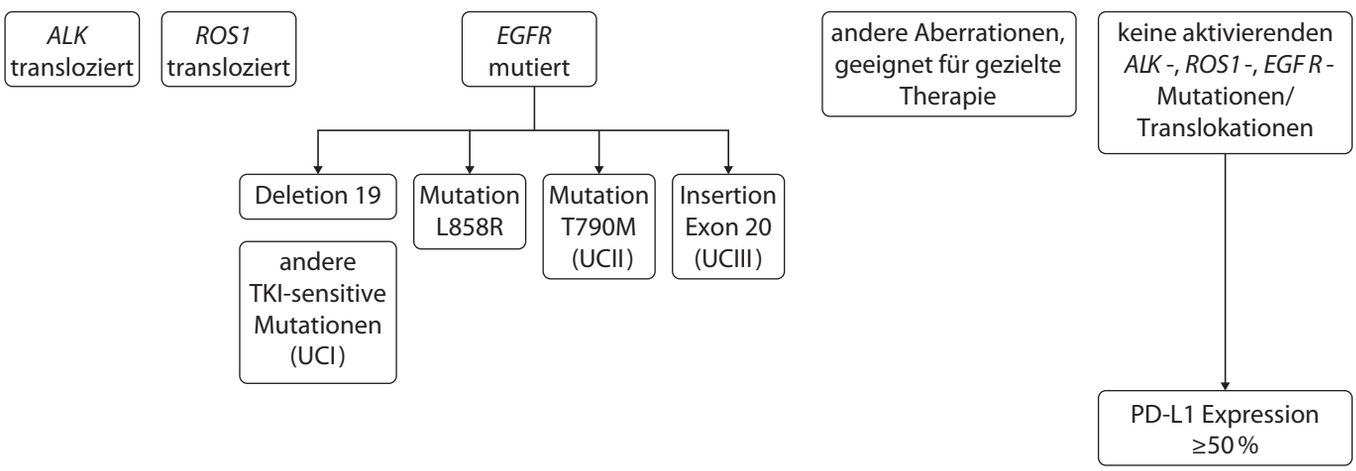
Diagnostics

Medical history and physical examination

Diagnosis of every disease begins with a comprehensive medical history, identification of clinical symptoms, and physical examination. However, during medical history the current state of knowledge should also be considered. Even experienced physicians must re-evaluate their extensive and proven behaviour self-critically again and again. An example in the field of oncology is the relatively new topic of secondary neoplasms. These are not metastases of a diagnosed primary tumour, but neoplasms in another organ, sometimes even in the same organ, e.g. breast. At present, some 17 per cent of all patients with newly diagnosed cancer already have another malignant disease[1]. The type of secondary neoplasm is causally connected with the primary disease, mainly due to the persisting risk factors, e.g. hereditary predisposition, smoking, and increasing age. Antineoplastic therapy is an additional risk for secondary neoplasms. Radiation and cytostatic therapy with alkylating agents and topoisomerase II inhibitors can induce malignancies especially in young patients[2]. The previous history of a secondary neoplasm is somatically significant because of potential long-term consequences of the primary neoplasm therapy. This history also has an essential

Molekulare und immunhistochemische Klassifikation des nichtkleinzelligen Lungenkarzinoms [3]

fortgeschritten / metastasiert - Diagnostik



Quelle: Prof. Dr. med. Bernhard Wörmann

Abbildung 1: Am Beispiel des Lungenkarzinoms lässt sich der rasante Wandel von Diagnostik und Therapie illustrieren.

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influence on the patient's dealing with the cancer recurrence.

Pathology

Nowadays, cancer is not only one disease, but hundreds of various diseases and disorders – each with its unique features. The rapid change becomes apparent in the example of lung cancer, which was divided into two major diagnoses until recently (small cell lung cancer and non-small cell lung cancer). Today, it is categorised into at least two dozens of genetically different entities some of which can be treated. Figure 1 shows the present diagnostic algorithms of non-small cell lung cancer[3].

A similar approach has long been established for pati-

Bildgebende Diagnostik des Prostatakarzinoms [8]

prädiktive Diagnostik – Beispiel Prostatakarzinom

	niedriges Risiko	mittleres Risiko	hohes Risiko
Primärtumor, cT	cT1/2a	cT2b	cT2c/3
	und	*oder*	*oder*
PSA-Wert in ng/ml	≤10	>10 bis ≤20	>20
	und	*oder*	*oder*
Gleason Score	≤6	7	≥8
weitere Diagnostik	**keine**	**evtl. Skelettszintigraphie**	**MRT oder CT-Becken Skelettszintigraphie weitere Symptom-orientierte Diagnostik**

Quelle: Prof. Dr. med. Bernhard Wörmann

Abbildung 2: Empfohlenes Vorgehen beim lokal Prostatakarzinom.

ents with breast cancer with classification into molecular subtypes (luminal A, etc.) [4, 5]. In the field of oncology, microscopic characterisation of malignant diseases is more and more replaced by complex biological diagnostics using molecular genetic and other procedures. This leads to a fundamental change in the classification of cancer diseases. The traditional organ reference was amended and partly replaced.

One critical question is which pathology parameters should be determined. Possibilities are almost unlimited, e.g. by means of whole genome sequencing. Current specification is based on the therapeutic consequence (see Figure 1). This focussing on predictive markers excludes many prognostic markers. This presents a high conflict potential, e.g. in case of acute myeloid leukemia (AML). The current classification of AML comprises more than 25 morphologically and genetically characterised subgroups[6], the majority of which are not predictive. For the use of the recently launched midostaurin, molecular determination of FLT3-mutations is required which is not part of the WHO classification[7].

Imaging, laboratory, and further diagnostics

Guidelines also provide provisions for further diagnostics, the so-called staging. They are guided by the probability of the proof of pathological findings, e.g. local infiltration or

metastases, and the resulting therapy[8, 9]. Figure 2 shows the recommended approach for localised prostate cancer.

It shows the initially established parameters of imaging (CT), laboratory diagnostics (PSA), and pathology (Gleason) including the resulting recommendations for risk-adapted diagnostic imaging. The basic concept is to avoid over-diagnosis and focus on predictive examinations. This will not always correspond to the patient's wishes and the physician's reality. Many patients would accept comprehensive diagnostic imaging, e.g. whole-body MRI or PET, even for localised stages of non-aggressive tumours, and ask for it to obtain highest possible safety.

Therapy

Therapy goal

Decision making begins with the patient. During the initial contacts, the physician must capture the living conditions of the respective patient. A 20 year old patient with Hodgkin's lymphoma will not have any discrepancy with his physician, as therapy will be all about healing while avoiding long-term side effects to the greatest possible extent. In contrast, a 85 year old patient with metastastic prostate cancer might have different expectations, i.e. therapy will primarily be about prolongation of his life, alleviation of suffering, or avoidance of stressful symptoms.

Current state of knowledge

At present, the field of oncology is very dynamic. In recent years, one new pharmaceutical or indication was approved every month by the European Medicines Agency (EMA) on average. Treatment recommendations for metastatic prostate cancer show the fundamental changes in the recommendations during the past four years. Figures 3a and 3b show a comparison of the algorithms used in 2014 and 2018, respectively, including integration of the findings from the early benefit assessment of second line treatment of castration resistant prostate cancer.

Such a development is characteristic for most areas of oncology. New pharmaceuticals are first tested in patients with recurrent/refractory cancer and approved for second or third line treatment. If the pharmaceutical has proven to be efficient and safe, studies with patients in early disease stages up to a primary (neoadjuvant) or adjuvant situation will follow. Not all of these studies at early therapy stages achieve the desired end point, in case of metastatic prostate cancer they were successful. In addition, relevant data of an independent study was available:

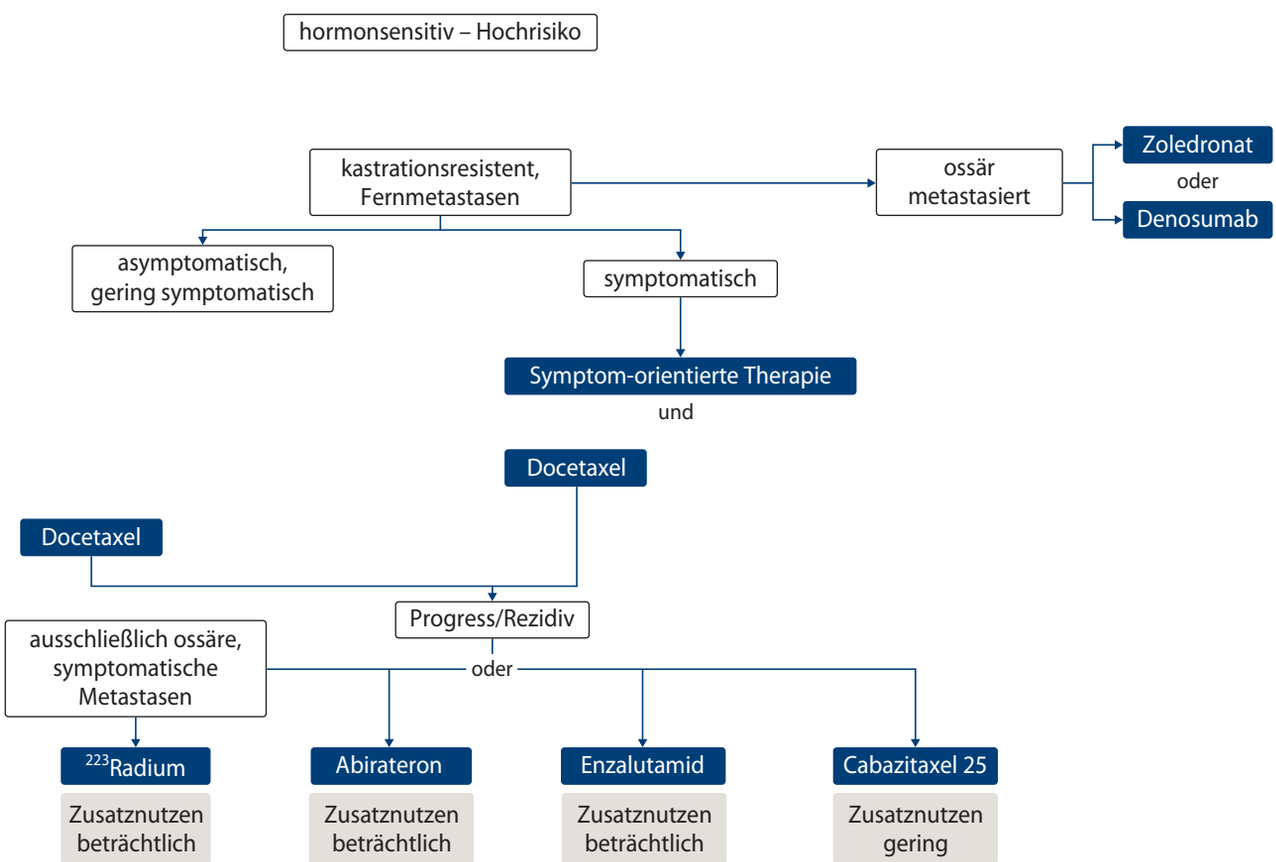
- In 2016, abiraterone was approved for first-line treatment of castration-resistant prostate cancer with „significant" additional benefit. Moreover, it was approved for the treatment of high risk patients with metastatic, hormone-sensitive prostate cancer in 2017; the procedure of early benefit assessment has not yet been completed.
- In 2016, enzalutamide was approved for first-line treatment of castration-resistant prostate cancer with „significant" additional benefit;
- Findings of a large randomised study published in 2017 show that cabazitaxel is also efficient at a dosage of 20 mg/m^2 with a lower toxicity as compared to the dosage of 25 mg/m^2 used in the approval study[10].

The approval of pharmaceuticals in an early line of treatment has a major influence on their use in patients with recurrent/refractory cancer. Most of these pharmaceuticals are not or only insufficiently efficient for re-treatment, so that the findings from the early benefit assessment are or are likely to be no longer valid, respectively.

Efficiency – early benefit assessment

Efficiency is one component of the decision making para-

Systemische Therapie des metastasierten Prostatakarzinoms 2014 [8]



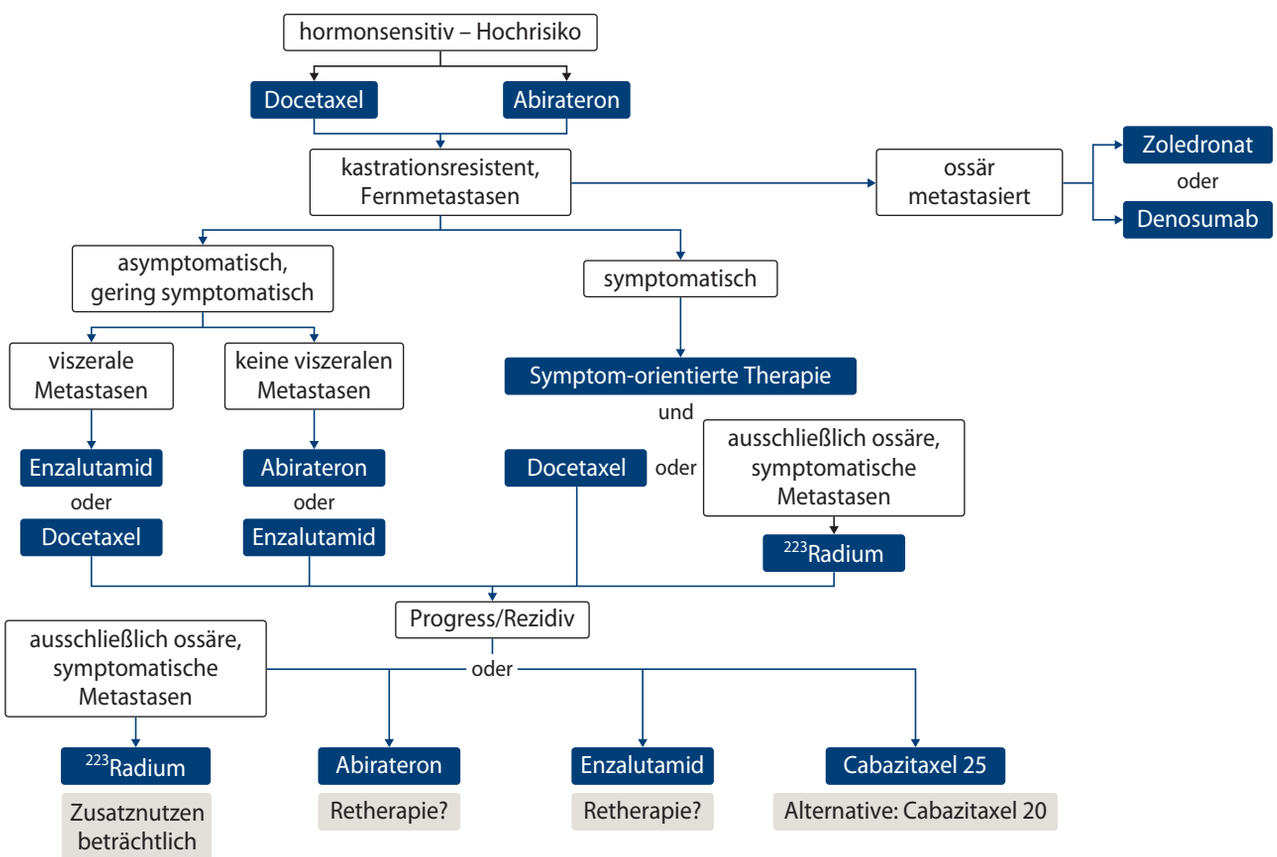
Quelle: Prof. Dr. med. Bernhard Wörmann

Abbildung 3a: Stand der Empfehlungen für die Therapie des Prostatakarzinoms im Jahr 2014.

meters for the physician. The determinations of the Federal Joint Committee (G-BA) within the scope of early benefit assessment of new pharmaceuticals form the basis for price negotiations between health insurance funds and pharmaceutical companies. In case of different evaluations of various subgroups, a mixed price is calculated and agreed upon. The legitimacy of this approach was questioned by the Berlin-Brandenburg Superior State Social Court [11] and is currently under discussion.

The prescribing physician must be informed about the context of the decisions to be able to consider the G-BA's determinations. So far, emphasis was placed on the follo-

Systemische Therapie des metastasierten Prostatakarzinoms 2018 [8]



Quelle: Prof. Dr. med. Bernhard Wörmann

Abbildung 3b: Stand der Empfehlungen für die Therapie des Prostatakarzinoms im Jahr 2018.

wing questions:

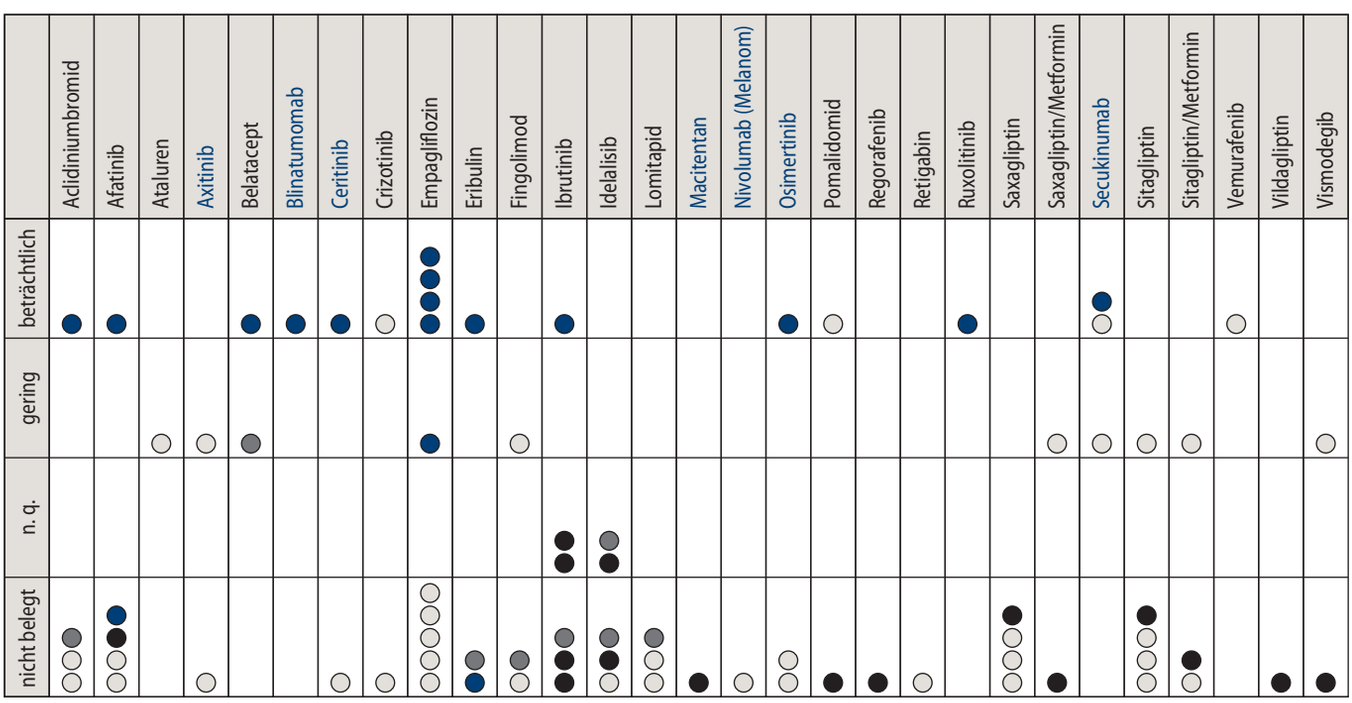
- Which subgroups have been defined?
- Which endpoints have been evaluated?
- Against which comparative treatment was the pharmaceutical evaluated?
- Does „additional benefit not proven“ mean a lack of superiority to the appropriate comparative treatment or lack of data for appropriate evaluation?
- Has the pharmaceutical received orphan drug status?

In the course of time the following question arises:

- Does the basis of the determination still correspond to the current state of knowledge?

Vergleich von Neu- zu Erstbewertungen in der frühen Nutzenbewertung [13]

Neubewertung 2011 – 2017



Neubewertete Arzneimittel aus dem Jahr 2017 sind blau, neubewertete Arzneimittel aus den Jahren 2011-2016 schwarz geschrieben.

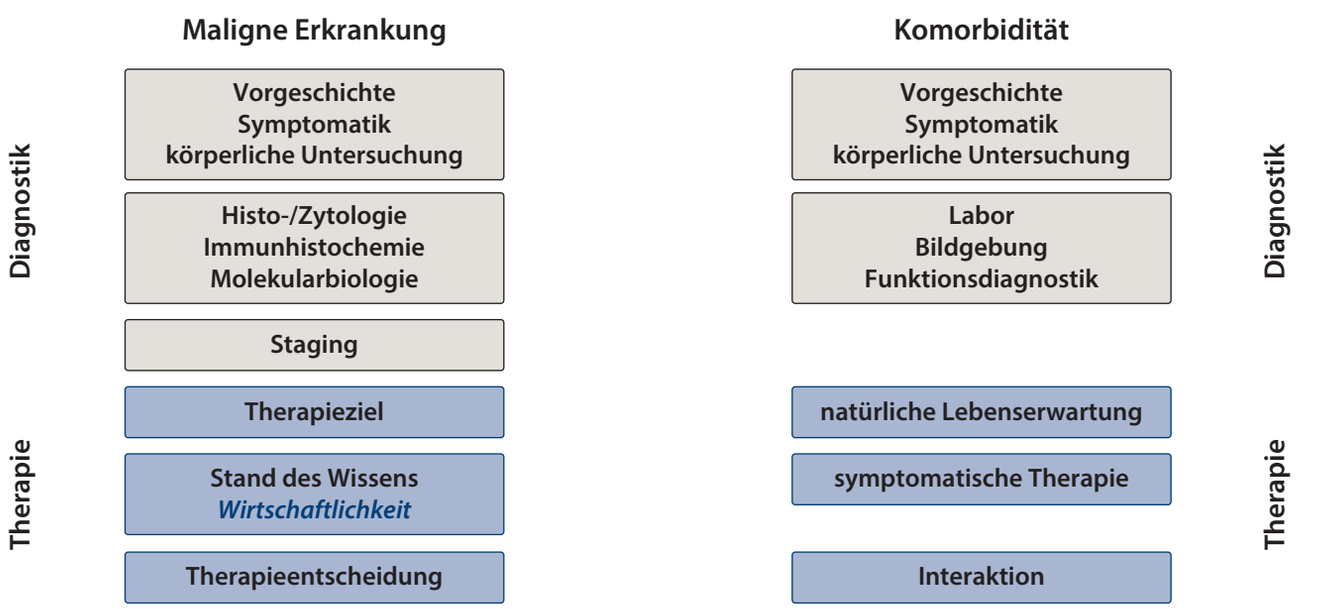
- keine Änderung gegenüber erster Bewertung
- höhere (bessere) Bewertung gegenüber erster Bewertung
- niedrigere (schlechtere) Bewertung gegenüber erster Bewertung
- Änderung der Definition der Subgruppe

Quelle: Prof. Dr. med. Bernhard Wörmann

Abbildung 4: Bei 45 Prozent der Neubewertungen durch den G-BA ist es zu Änderungen bei den Subgruppen gekommen.

An analysis of re-evaluations revealed certain changes that have taken place over time. By the end of 2017, the G-BA re-evaluated 29 pharmaceuticals[12, 13]. In the majority of the cases, this was due to the expiry of a time period stipulated during the first evaluation, in some pharmaceuticals with designated orphan drug status to an increase of sales volume to > 50 million Euros, and in individual cases to requests of the pharmaceutical company for re-evaluation. Figure 4 shows the re-evaluation of pharmaceuticals as compared to the respective initial evaluation. In 36 out of 80 subgroups (45 percent) there have been changes. In most of the cases (21 per cent), pharmaceuticals received a better evaluation, followed by changed definitions of subgroups (14 per cent), and worse evaluation (10 per cent).

Aufbau der Therapieentscheidung unter Berücksichtigung der Komorbidität



Quelle: Prof. Dr. med. Bernhard Wörmann

Abbildung 5: Komorbiditäten haben großen Einfluss auf Diagnostik, Therapie und Therapiebegrenzungen.

Comorbidity

Treatment of cancer patients is not possible without considering their comorbidity. The demographic development with an increasing number of elderly patients reinforces this trend. Several relevant, internal diseases have a major influence on diagnostics, treatment decision, as well as on their limitations. Figure 5 shows a graphical illustration of this situation.

Almost all elements of a treatment decision in the field of oncology can be represented likewise for the diagnosis and treatment of comorbidities. Interactions between various pharmaceuticals should also be considered in medical tumour treatment. These might both decrease and increase the effects of the pharmaceutical.

The figure shows that considering the efficiency of a certain prescription on the basis of the early benefit assessment by the G-BA (light blue) is a major, but only one element of the treatment decision in the field of oncology.

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Subgroup evaluation and mixed prices: Included in the AMNOG process

Wolfgang Kaesbach | Arbitration Board according to §§ 129 (8) and 130b (5) SGB V

Attentive observers of legislation on pharmaceutical supply were probably not surprised by CDU/CSU's and FDP's draft law on the reorganisation of the pharmaceutical market in Statutory Health Insurance (GKV) of 6 June 2010. Since 2001, the evaluation of the benefit and pricing of pharmaceuticals has been discussed („round table"), but (only) the benefit assessment was introduced at that stage (Statutory Health Insurance Modernisation Act, 2004). The complementary regulation for the stipulation of maximum amounts for non-referenceable pharmaceuticals on the basis of a benefit and cost evaluation was not adopted (Statutory Health Insurance Competition Strengthening Act, 2007). However, the speed of action was rather unusual for the executive power. Only four working days after AMNOG came into force, the Pharmaceutical Products Benefit Assessment Ordinance (AM-NutzenV), 28 December 2010) was issued and by amendment of its Rules of Procedure (20 January 2011), the Federal Joint Committee (G-BA) was fully operative within one month. The question raised in this article as to whether subgrouping and mixed pricing are stipulated in the AMNOG process can be answered with a clear „Yes" - and not only in the eighth year of AMNOG.

Subgroups versus subpopulations

Unfortunately, even professionals do not always use scientific terminology properly and speak of subgroups, although they mean subpopulations (also referred to as partial populations, patient groups). Although this is due to a certain degree of negligence, different terms are sometimes used intentionally in terms of polemical propaganda.

The pharmaceutical industry does not support the German methodology of benefit assessment using the argument that the G-BA created rather too many subgroups and it would be disproportionate and too complex to analyse them all in studies against active comparators for their legally-binding patient-relevant endpoints. Moreover, it would be impossible to present statistically significant evaluations at the time of early benefit assessment for some patient-relevant endpoints. In conclusion, „innovative" pharmaceuticals would be rated worse in Germany than in other countries where the benefit of new pharmaceuticals is also evaluated after approval.

The European Medicines Agency (EMA) provides the following definitions: The term „subgroup" is used to refer to a subset of a clinical study population. The term „subpopulation" is used to refer to a subset of the population described by the targeted therapeutic indication[1].

In other words: The sponsor who is ultimately responsible for the study design asks for a clinical analysis and evaluation of a variety of subgroups that are also considered during benefit assessment. However, the additional benefit is determined for the whole field of application or by subpopulation resulting from the approval and/or stipulation by the G-BA. According to the standards of evidence-based medicine, subpopulations must be defined, if the field of application comprises patients with a different treatment standard according to the generally accepted state of me-

dical knowledge. In a few exceptional cases, the extent of the additional benefit will be further differentiated on subgroup level (see Figure 2).

Subgroups and subpopulations as well as patient-relevant endpoints are already subject to an initial benefit assessment that the Institute for Quality and Efficiency in Healthcare (IQWiG) has published on behalf of the G-BA[2], i.e. the benefit assessment of clopidogrel versus acetylsalicylic acid (ASS) in the secondary prophylaxis of vascular diseases[3].

In the clinical studies that were used for the evaluation of the benefit, significantly more than ten predefined subgroups were identified and evaluated individually, i.e. gender, age groups, several comorbidities, several vascular risk factors, type of pretreatment and many more. However, the result of the benefit assessment was determined on the level of subpopulations as defined by the G-BA. In this case, an additional benefit (yes/no) was determined in two subpopulations: Long-term treatment with clopidogrel (monotherapy) provides an additional benefit for patients with symptomatic peripheral arterial occlusive disease as compared to ASS treatment. For patients with cerebrovascular disease and patients with coronary heart disease, an additional benefit of clopidogrel was not proven.

Since 2011, pharmaceutical companies must provide certain information in the value dossier of reimbursable pharmaceuticals with new active substances, including the number of patients and patient groups for whom a therapeutically significant additional benefit has been proven[4]. This may either be a patient group (identical with the approval population) or several patient groups (subpopulations). The Pharmaceutical Products Benefit Assessment Ordinance (AM-NutzenV) even assumes subpopulations by stating that during benefit assessment it is evaluated whether for the respective pharmaceutical (…) an additional benefit has been proven, for which patient groups, and to what extent (…)[5].

Based on the 228 evaluation procedures completed by the end of 2016, 486 subpopulations were created, i.e. an average of (only) 2.13 subpopulations per procedure[6]. So, given these figures, complaining about a filigration of the approved field of application is nothing but unjustified criticism.

In 2005, mortality, morbidity, and quality of life were already mentioned several times in the first Methods Paper of the IQWiG as patient-relevant endpoints[7]. In the benefit assessment of clopidogrel versus ASS, the following patient-relevant therapeutic goals were evaluated: Reduction

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of vascular-specific mortality, reduction of vascular-specific morbidity, reduction of adverse drug reactions, and improvement of disease-related quality of life[3]. Two months after publication of this benefit assessment, patient-relevant endpoints were first mentioned in the law (Economic Optimisation of Pharmaceutical Care Act, AVWG). Thus, in order to furnish proof for a therapeutic improvement within the scope of the reference price system (…) direct comparative studies with other pharmaceuticals (…) with patient-relevant endpoints, primarily mortality, morbidity, and quality of life should be considered[8].

The AM-NutzenV contains the same wording, i.e. for reimbursable pharmaceuticals with new active substances that are pharmacologically-therapeutically comparable to reference price pharmaceuticals, the medical benefit must be proven as therapeutic improvement[9]. In 2007, patient-relevant endpoints were placed in the context of the evaluation of the benefit and costs of pharmaceuticals and specified in the Statutory Health Insurance Competition Strengthening Act (GKV-WSG): In terms of patient benefit, especially the improvement of the physical condition, reduction in duration of the disease, prolongation of survival time, reduction of side-effects, as well as improvement of the quality of life should be given due consideration[10]. The AM-NutzenV contains the same wording, i.e. patient-relevant therapeutic effect for the determination of the benefit of a certain pharmaceutical[11].

Preliminary conclusions on subpopulations

The formation of subpopulations and their evaluation was already subject of a comparative assessment of the benefit of clopidogrel versus ASS by the IQWiG in 2006. The conclusion then was essentially prototypical for G-BA decisions about benefit assessment as of 2011 (see Figure 1). A critical vulnerability of the benefit assessment in the period before AMNOG was the legal procedural specifications, especially the „facultative provision", obligation of the G-BA to examine, as well as the application of all provisions relating to the entry into force of decisions, rendering the evaluation of all newly prescribable pharmaceuticals with patent-protected active substances as well as other significant pharmaceuticals impossible[12].

Thus, subgroups, subpopulations, patient-relevant endpoints did not appear from nowhere and did not catch pharmaceutical companies unprepared in 2010. Germany was indeed one of the last countries to introduce benefit assessments in Europe. Institutions with comparable tasks, e.g. the National Institute for Clinical Excellence (NICE) for the National Health Service in England and Wales which was founded in 1999 or the Haute Autorité de Santé (HAS) in France which was founded in 2004 work on the same basis of evidence-based medicine like the IQWiG and G-BA. A closer look at the regulatory environment should have led to the conclusion that the era of „business as usual" is over and that pharmaceutical approval would only be a mandatory yet not necessarily sufficient condition for reimbursement by national healthcare systems.

The path to the reimbursement amount

Germany is one of few countries in the world where newly approved pharmaceuticals are generally prescribable upon market entry by the national healthcare system – and even reimbursable at the price stipulated by the pharmaceutical company. In 1989, this kind of „shopping list" was first limited with the introduction of reference prices in statutory health insurance for comparable pharmaceuticals as defined by certain statutory criteria serving as a limit for reimbursement by the statutory health insurance funds. In 2017, savings of 7.7 billion Euros were achieved through the application of reference prices without sacrificing quality of patient care[13].

Against the background of the draft decision of the Federal Social Court to the Federal Constitutional Court, whether the power to determine reference prices for pharmaceuticals which has been granted to the National Associations of Health Insurance Funds, is in accordance with the German constitution, as well as that by the Düsseldorf Higher Regional Court and Federal Supreme Court to the European Court of Justice, whether insurance funds should be considered as associations of undertakings in connection with the determination of reference prices as defined in Article 81 EC, a „round table" was entrusted with the task to develop various proposals for the further development in pharmaceutical care. One proposal involved the presentation and comparative assessment of the benefit as well as health economic evaluations of the cost-benefit ratio in order to determine a maximum reimbursement amount. These recommendations were not supported by the major national associations of pharmaceutical companies, i.e. vfa, BPI and BAH as well as ABDA (pharmacists), on the grounds that a reasonable reaction of the market to the results of the benefit assessment could be expected [14].

In 2007, the Statutory Health Insurance Competition Strengthening Act (GKV-WSG) made up what the legislator couldn't realise with the GMG. In order to limit the costs of pharmaceuticals without reference price, the former National Associations of Health Insurance Funds should now jointly determine maximum amounts according to Section 213 SGB V on the basis of a cost-benefit assessment. Alternatively, maximum amounts could also have been stipulated in consultation with the pharmaceutical company [15].

As mentioned above, the regulation for the stipulation of maximum amounts was not adopted. Although the G-BA added provisions for the cost-benefit assessment of pharmaceuticals to the 4th Chapter of the Rule of Procedures on 16 July 2009, the IQWiG published General Methods for the Evaluation of the Relationship between Cost and Benefit – version 1.0 on 19 October 2009, and the G-BA issued initial orders in the meeting of 17 December 2009, it

Nutzenbewertung 2006 übersetzt in fiktives Verfahren nach AMNOG

■ neuer Wirkstoff	Clopidogrel (Plavix®, Iscover®)
■ zugelassenes Anwendungsgebiet	Sekundärprophylaxe vaskulärer Erkrankungen
■ zweckmäßige Vergleichstherapie	Acetylsalicylsäure
■ ZN im Verhältnis zur zVT	
• Subpopulation A	Patienten mit symptomatischer pAVK • Zusatznutzen belegt
• Subpopulation B	Patienten mit ZVK und KHK • Zusatznutzen nicht nachgewisen

Quelle: Wolfgang Kaesbach

Abbildung 1: Die Bildung von Subpopulationen war bereits Gegenstand der Bewertung von Clopidogrel versus ASS.

was already agreed in the coalition agreement of the newly elected conservative-liberal government on 24 October 2009 that the procedures for the determination of prices for pharmaceuticals should be reviewed. The latter was mainly due to the fact that the model of efficiency limits developed by the IQWiG was criticised by „leading" German health economists who wanted to include other areas of expenditure beyond statutory health insurance into the cost-benefit assessment.

What was meant to be an exception in the GKV-WSG, now became the rule with AMNOG: pharmaceutical companies and the GKV-SV shall determine reimbursement amounts for all newly prescribable pharmaceuticals with patent-protected active substances on the basis of the respective G-BA decision and benefit assessment to replace the introductory price from the 13th month onwards after the pharmaceutical has been placed on the market. Like for other collective agreements regulations in the field of social legislation, an arbitration board is asked to determine the reimbursement amount as well as other controversial points of the agreement in accordance with Section 130b Paragraph 1 Sentence 1 SGB V if negotiations fail.

For pharmaceuticals with proven additional benefit, the reimbursement amount is agreed as a surcharge to the annual treatment costs of the appropriate comparative treatment (ACT)[16]. In addition, the actual sales prices in other European countries (decision by the arbitration panel on the basket of countries dated 8 March 2012) as well as annual treatment costs of comparable pharmaceuticals shall be considered[17]. For pharmaceuticals without additional benefit, a reimbursement amount shall be agreed upon that does not increase the annual treatment costs as compared to the ACT[18].

For pharmaceuticals without proven additional benefit, a reimbursement amount shall be determined that results to reasonably reduced annual treatment costs as compared to the ACT[19]. For pharmaceuticals with a smaller benefit as compared to the ACT, the reimbursement amount shall be agreed as a markdown of the annual treatment costs of the ACT[20].

Mixed price

Regarding the question raised in this article and the preliminary conclusion on subpopulations, it should be mentioned that the contractual partners have transferred the codified provisions of the law and framework agreement from the beginning for the determination of a reimbursement amount on pharmaceutical level to the patient groups defined by the G-BA combining partial reimbursement amounts to one mixed price for the pharmaceutical which can be identified via the central pharmaceutical number. The legal framework leaves no scope for the (ongoing) demands especially by the industry that if an additional benefit has been proven for (only) one subpopulation, the determination of the reimbursement amount for subpopulation(s) without additional benefit should also be based on the principles and criteria for a pharmaceutical with additional benefit.

Thus, it was a lucky coincidence which affected the further implementation that for the first pharmaceutical that underwent the AMNOG procedure, i.e. Brilique® with the new active substance ticagrelor, a practicable solution had to be found in terms of subpopulations and mixed prices. After the G-BA decision of 15 December 2011, a significant additional benefit was proven for two patient groups (unstable angina pectoris and non-ST-segment elevation myocardial infarction, NSTEMI), while an additional benefit was not proven for three patient groups with STEMI but different treatment.

One complicating issue is that the G-BA determined

three ACTs with different prices for the five subpopulations. Thus, in the subpopulation of STEMI patients with percutaneous coronary intervention, one indication was identified for a non quantifiable additional benefit in two of the predefined subgroups of the TRITON study used for benefit assessment (patients = 75 years, unsuitable for the ACT with prasugrel plus ASS as determined by individual benefit risk assessment, as well as patients with previous transitory ischaemic attack or ischaemic stroke) and the G-BA did not quantify the number of patients in the subgroup with TIA or ischaemic stroke (see Figure 2). Despite this challenging situation, the contractual partners were able to agree on a reimbursement amount in form of a mixed price [21].

Meanwhile, for the 166 active substances and active substance combinations that are available on the market, reimbursement amounts have been negotiated (135) and fixed (28), respectively. In three cases, preservation of an arbitrated reimbursement amount has been contractually agreed upon[22]. It is not surprising, that reimbursement amounts are also criticised. On the one hand, it is sometimes difficult to reconcile the amount of the reimbursement on the basis of the G-BA decision: Prices are established like in a „lottery", regardless of the extent of the additional benefit as determined by the G-BA[23]. On the other hand, the question is whether an economic mixed price can be negotiated at all or whether prescription of a pharmaceutical at the reimbursement amount is always an economic solution: The amount that is „globally" considered economic can be uneconomic in individual cases[24] and a uniform reimbursement amount might not be equally economical for all patient groups[25].

Can an economic mixed price be negotiated?

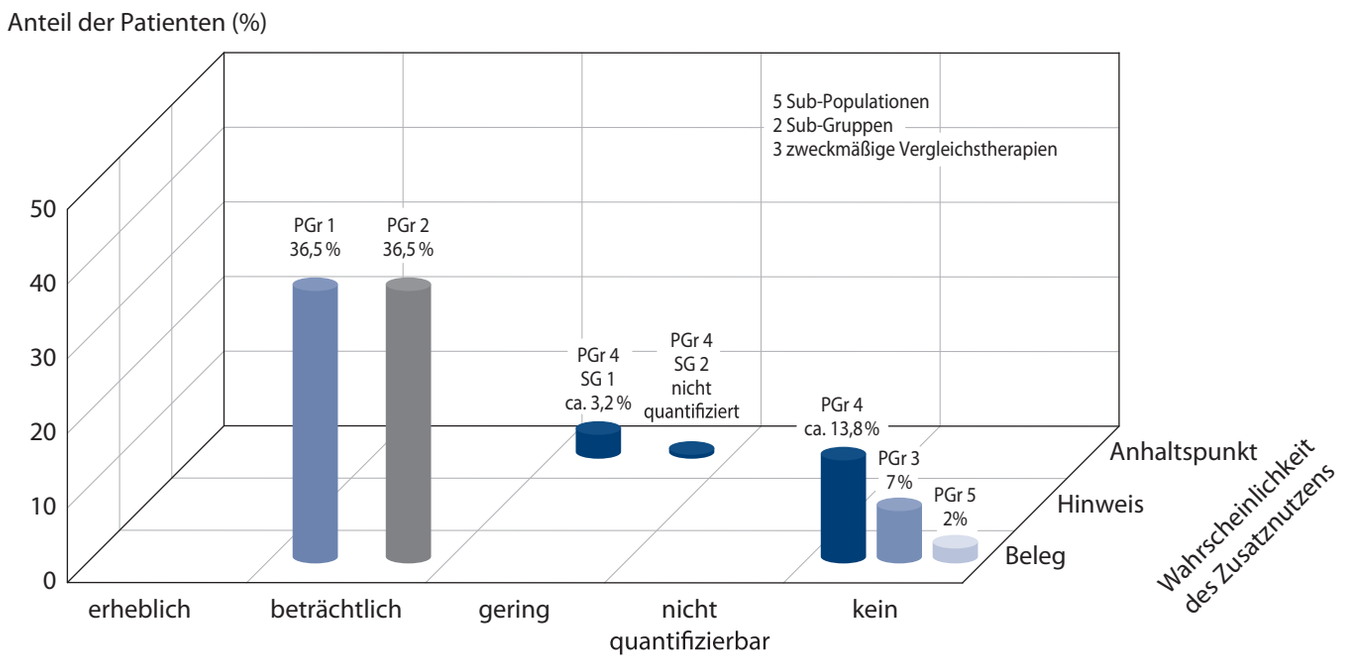
For the sake of simplicity, we assume that the G-BA decision includes both patient groups „with" and „without" additional benefit. Qualifying information regarding the extent and probability of the additional benefit are not required, as these characteristics do not have an influence on the principle question „mixed price yes or no". For instance, for the active substance axitinib, the G-BA determined the subpopulation without additional benefit to be 480 to 2,400 patients and the subpopulation with additional benefit at three to six patients, respectively[26]. The smaller the share of patient group(s) with additional benefit of the overall approval population (in this case 0.3 percent), the better the reimbursement amount must be aligned with the costs (generally less expensive) of the appropriate comparative treatment for the patient group(s) without additional benefit.

If the reimbursement amount is agreed upon by mutual agreement (and if the pharmaceutical company continues to distribute the pharmaceutical), even despite other contractual provisions, the negotiation result will probably tear down the bar of the efficiency principle according to Section 12 SGB V.

Can prescriptions at the mixed price be economical?

Any pharmaceutical that is available on the market is prescribable in accordance with the approval. Even the division of the approval population into partial populations by the G-BA within the scope of a subsequent benefit assessment does not change this fact. With regard to the mentioned 228 completed procedures, about one quarter of the patients have a proven additional benefit[6]. Thus, a mixed price is always too low for patient groups with an additional benefit and always too high for patient groups without additional benefit. However, prescriptions at a mixed price

Bei Sub-Populationen ist der Erstattungsbetrag ein Mischpreis



Quelle: G-BA-Beschluss zum Wirkstoff Ticagrelor vom 15.12.2011 (BAnz. Nr. 11, Seite 254 vom 19.01.2012)

Abbildung 2: Die Bildung des Erstattungsbetrags für Ticagrelor war prägend für die weitere Umsetzung des AMNOG.

would neither present a burden nor a relief for paying parties, if the proportional distribution of the prescriptions correspond to the number of patients defined by the G-BA decision. It is common knowledge that insufficient epidemiological data are available in Germany so that reliable prognoses are virtually impossible. Thus, patient numbers in the G-BA decision are often referred to as ranges with frequently extreme limits. Results of health insurance fund-related settlement data suggest that the actual prescription environment differs (in some cases significantly) from epidemiologically-derived patient shares. In order to ensure efficiency of the negotiated or fixed mixed price in line with patient numbers of the G-BA within acceptable limits, current prescription shares with potentially individual reimbursement procedures should be reviewed regularly [27].

Mixed price in terms of the Berlin-Brandenburg Superior State Social Court (LSG)

Once and for all: The LSG did not decide on the mixed pri-

ce[24]: Their only significant consideration is, that arbitration in accordance with Section 130b SGB V must always outline the calculation used for the determination of the reimbursement amount in a transparent and plausible way with all its implications[28]. However, in his judgement with non-significant considerations the senate referred to the mixed price as a so-called obiter dictum. The Federal Social Court is expected to hear the appeal within the scope of revision in the course of 2018 (B 3 KR 20/17 R). It remains to be seen whether and how the Federal Social Court (BSG) will address the issue of mixed prices. If the BSG does not address this issue, there is no need to legislate.

There are sufficient options for the self-governing bodies to find appropriate individual solutions:

- on the level of the G-BA by restriction or exclusion of prescription for application fields without additional benefit in Annex III of the AM-RL[29]. However, it should be considered that the physician can prescribe excluded pharmaceuticals in medically justified individual cases [30]. Moreover, decisions on the benefit assessment on the one hand and prescribability on the other hand cannot come into force simultaneously due to different procedural specifications;
- on federal or regional level by „additional benefit"-oriented prescription control within the framework specifications according to Section 84 Paragraph 6 SGB V or in regional agreements for pharmaceuticals according to Section 84 Paragraph 1 SGB V, respectively;
- on the level of the contractual partners according to Section 130b SGB V by flexibilisation of the agreement on the reimbursement amount according to Section 130a Paragraph 1a SGB V as amended by the AM-VSG.

Preliminary conclusions on the mixed price

Since the introduction of AMNOG in 2011, the reimbursement amount for a pharmaceutical is determined on the basis of the G-BA decisions by means of the benefit assessment for patient groups with and without additional benefit. The widespread claim that came up for immediate clarification by the legislator after the decision of the Berlin-Brandenburg Superior State Social Court about the case of interim measures[31] to avoid jeorpadising the supply of patients with new active substances as a consequence of the physicians' fear of recourse was not only too early, but also promoted the general feeling of insecurity.

After the clarifying decision, mixed prices remain negotiable and can be fixed by the arbitration board, provided that their justification meets the legal requirements. However, even the legislator cannot fulfil the physicians' expectation that prescriptions at the mixed price would always be economic within their range of approval, because the efficiency of a prescription can only be evaluated on an individual basis. The hasty call for the legislator is indeed not risk-free, as very detailed regulations are rather a treasure trove for lawyers than ensuring a legally-binding implementation. However, the lack of creative drive or power of the self-governing bodies presents a higher existential threat.

Shall subpopulations and mixed price be included in the PIS?

During consultations on the GMG, politics already expressed the intention to use the additional benefit assessment to avoid prescription of pharmaceuticals in cases where no significant therapeutic improvement can be achieved as compared to pharmaceuticals that are normally prescribed [32]. If the G-BA subdivides the approval population into vari-

ous patient groups, prescription limitation to patient groups with additional benefit would be considered preferable to a „total" exclusion of the pharmaceutical from prescription (where applicable).

According to Section 92 Paragraph 1 Sentence 1 SGB V, the G-BA is authorised to do both. In contrast, the legal obligation of the G-BA to publish its decisions about the benefit assessment in machine-readable form for electronic programmes[33] is only an informational service that does not at all limit reasoned treatment decisions by prescribing physicians.

We expect a clarifying regulation within the next months[34]. It is important that its subsequent implementation does not extend over several years like the integration of the requirements in the PIS on which the contractual partners have agreed upon for recognition and in case of prescription control procedures in consideration as peculiarity according to Section 130b SGB V. KBV and GKV-SV have first realised this on 1 October 2017 with a pharmaceutical-related feature and linking GKV-SV website. Since 1 April 2014, the reimbursement amount that was initially agreed as a rebate on the sales price of the pharmaceutical company and passed through all levels of trade, is the „new" sales price that serves as the basis for trade adjustments according to the pharmaceutical price regulation [35]. These prices have already been integrated via their central pharmaceutical number in the pharmaceutical data base of the respective practice management system.

Outlook

The determination and evaluation of the additional benefit in subpopulations as compared to an appropriate comparative treatment with subsequent agreement of a reimbursement amount as a mixed price based on the G-BA decision between the pharmaceutical company and the GKV-SV or – in case of disagreement – stipulation by arbitration are not only provided for in the AMNOG process, but are also applied as required.

However, the GKV's performance which is characterised by the efficiency principle according to Section 12 SGB V requires this also against the background of mixed price inaccuracies with regard to a reasonable cost neutrality that can never be excluded with (non-public) reimbursement amounts differentiated on subpopulation level. Implementation would be complex and only possible with a certain time lapse, as the structural basis and technical processes would have to be established first. The Federal Social Court should be aware of this before addressing the issue of mixed prices.

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Empirical findings on the mixed price

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The legal basis of the common practice of mixed pricing was recently questioned and, thus three alternatives were discussed: Prescription exclusions, indication-specific prices and further development of the „traditional" mixed price. So far, the mixed price discussion is quite theoretical and of legal nature. And the weighing assumptions used for mixed pricing have not yet been empirically verified. This is often not possible due to the lack of traceability of the subpopulations created by the G-BA in the claims data of statutory health insurances. However, analysis of one third of all pharmaceuticals with mixed price shows that the prevalence in the individual subpopulation as estimated by the G-BA approximately reflects the situation in outpatient care.

Mixed price in routine benefit assessment

1.1 Formation of a mixed price

Reimbursement amounts for new pharmaceuticals are negotiated between the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and the pharmaceutical company on the basis of the results of the early benefit assessment. They are based on the additional benefit for all patients in the approved field of application. The legal regulation of benefit-oriented pricing in Section 130b SGB V requires that the reimbursement amount reflects the result of the early benefit assessment and one price must only be negotiated, if it leads to higher annual treatment costs as compared to other comparable pharmaceuticals, if an additional benefit has been proven.

However, the additional benefit can vary for various patient groups. It includes cases in which both an additional benefit was identified or not for subpopulations within a certain field of application or an additional benefit of different extent was determined. Moreover, various appropriate comparative treatments (ACT) for each partial indication must also be taken into consideration with different annual treatment costs in various subsections that should be used as price reference.

A mixed price is required that either reflects the different additional benefit or the different price level, as Section 78 Paragraph 3 AMG (Medicinal Products Act) does not include a price differentiation via the central pharmaceutical number. From today's perspective, benefit-based pricing is only reliable for active substances with an approved indication and homogeneous target population. In the absence of proper legislation, the determination of some form of weighted „mixed price" is still common practice to date. By the end of 2017, for every fourth active substance

that had previously undergone benefit assessment (26 percent, n=49) a mixed price had to be negotiated due to the fact that the additional benefit has only been proven for part of the application field (cf. Figure 1).

1.2 Practical implementation of a „mixed price"

For a proper weighting of subpopulations in a mixed price, certain factors are required that fairly reflect the relevance of the respective subpopulation. At present, this adjustment can be made ex ante, i.e. prospectively for a contractual period, or ex post and thus retrospectively for a predefined period:

Ex ante: Evaluation of individual price components in the mixed price

- Prevalence as estimated by the G-BA
- „Weak factors" (e.g. expected market penetration).

Ex post: Retrospective continuous adjustment of the mixed price

- To date (presumably) only by means of contract termination and re-negotiation.

It can be assumed that for an ex-ante weighting, the prevalence indicated in the G-BA decision will be used as the best available information about the potential price relevance of the respective evaluation results. However, the prevalence is normally based on an estimated morbidity (e.g. on the basis of routine data from statutory health insurances) and is highly uncertain. This is reflected by the fact that the G-BA only quantifies the number of patients

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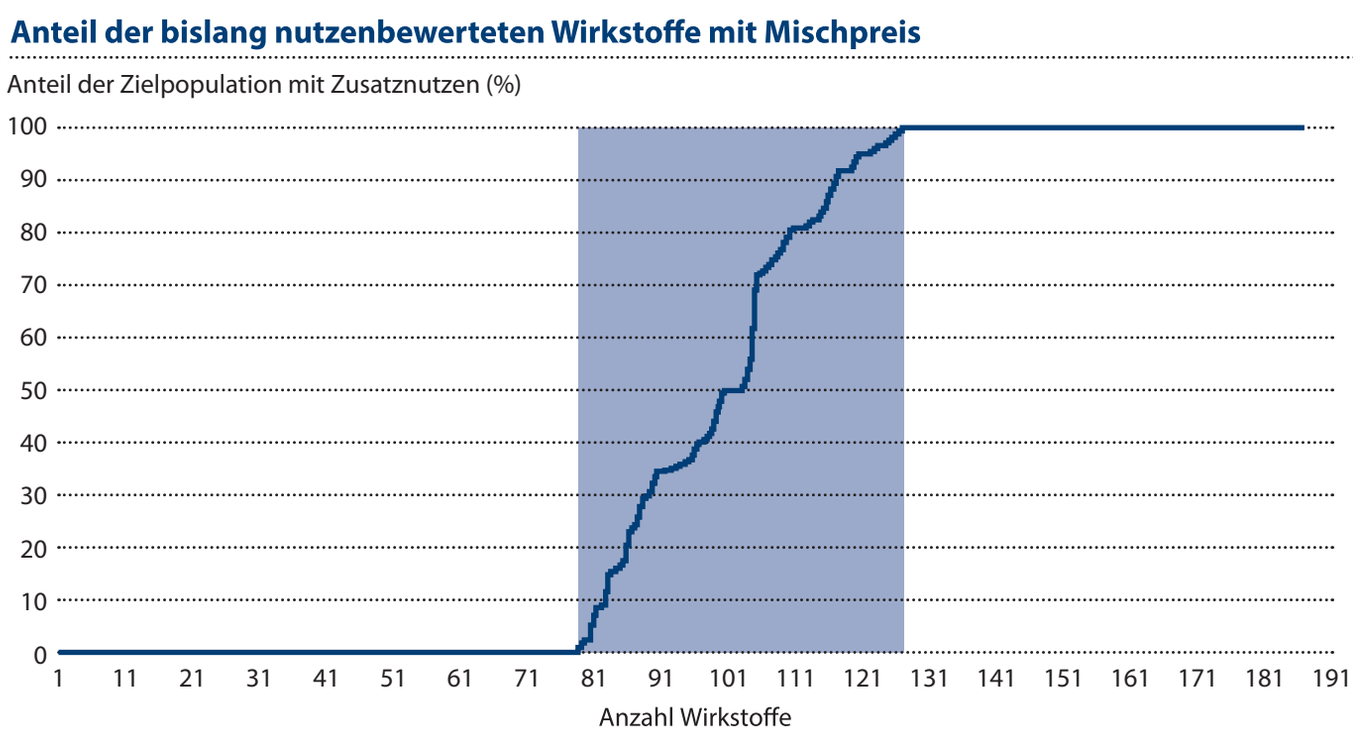


Quelle: Prof. Dr. Wolfgang Greiner, Julian Witte Lehrstuhl für Gesundheitsökonomie und Gesundheitsmanagement, Universität Bielefeld
Stand: 31.12.2017

Abbildung 1: Bis Ende 2017 ist für jeden vierten nutzenbewerteten Wirkstoff ein Mischpreis festgelegt worden.

as a range in 55 percent (n=310) of all evaluated populations or subpopulations until end of 2017. This particularly applies to subpopulations used for the calculation of the current mixed prices. In 70 percent (160/229) of all subpopulations that have been created for mixed prices, the G-BA did not quantify the respective prevalence as an estimate, but only indicated a range. In fact, in 62 of these subpopulations the G-BA did not provide an estimate, but only indicated a range for several subpopulations. A mixed price that has been determined on this basis, will inevitably reflect this uncertainty. Moreover, cross-procedural inconsistencies about the extent of the estimated prevalence were discussed (Ten Thoren et al. 2016). In principle, agreements can also be made irrespective of the prevalence, e.g. based on expected market shares. In the past, the arbitration board has used these agreements explicitly as weighting factors (cf. arbitration award on albiglutide (Eperzan®) that was reversed by the Berlin-Brandenburg Superior State Social Court). However, this factor might be even more unpredictable and only suitable for weighting of subpopulations in certain cases.

1.3 Why is there so much criticism about the mixed price?

There are three reasons why current mixed pricing has conflict potential:

1. Prescription rates deviating from the quantity weight of the mixed price do result in non benefit-related price distortions (LSG Berlin Brandenburg, Ref. L 9 KR 213/16, Haas et al. 2016).

2. Differentiation of subpopulations is not always appropriate or supported by scientific evidence (Rasch, Dintsios 2015).

3. In many cases, refusal to grant an additional benefit is not based on the best available evidence (Frick 2015).

„Non benefit-related price distortions"

If a physician prescribes a pharmaceutical in a subpopulation, for which an additional benefit has not been granted, efficiency of the prescription is controversial (GKV-Spitzenverband 2017). This is inevitable with a mixed price, as this will not result in increased annual treatment costs as compared to comparative pharmaceuticals on average, i.e. in a theoretical population, but possibly in the individual case.

In a landmark judgement that has attracted much attention, the LSG Berlin-Brandenburg made several statements about the legality of mixed pricing and criteria used for monetisation of additional benefits. Essentially, the LSG declared the mixed price for the GLP-1-analogue albiglutide unlawful (LSG Berlin Brandenburg, Ref. L 9 KR 213/16). According to the court, there are considerable doubts about the legitimacy of mixed pricing as it is currently practised, as it does not reflect a benefit-oriented reimbursement and would thus have no legal basis. Thus, it could lead to non-benefit-oriented price distortions, as it is

- unfavourable for statutory health insurances in case of proportionately higher prescription rates in the subpopulation without proven additional benefit,
- unfavourable for the pharmaceutical company in case of proportionately higher prescription rates in the subpopulations with proven additional benefit, and
- unfavourable as potential ACT for future benefit assessments and price determinations.

However, the standard in Section 130b Paragraph 3 Sentence 1 SGB V that constitutes the essential basis of the LSG's reasoning and according to which the reimbursement amount for a pharmaceutical without additional benefit must not result in higher annual treatment costs than the ACT, only applies for price determinations in cases where an additional benefit has not been proven for the whole field of application (Huster 2017).

Subpopulations in G-BA's procedures

A fundamental problem of mixed pricing is the common practice of creating subpopulations. In more than half of all benefit assessment procedures, the G-BA creates subpopulations divided into an average of 3.2 patient groups (with decreasing tendency, however). In addition, there may be approvals in new application fields. G-BA benefit assessment decisions about active substances with a mixed price have an average of 4.8 subpopulations or subsections of application. According to the decision, the subsections of application created by the G-BA include 128,000 patients on average (median of 8,450). In 25 percent of the previously created partial fields of application, the prevalence as estimated by the G-BA is less than 1,000 patients (cf. Figure 2). One possible interpretation is that with a lower number of especially very small subpopulations the problem of mixed pricing could at least partially be solved.

Additional benefit not proven

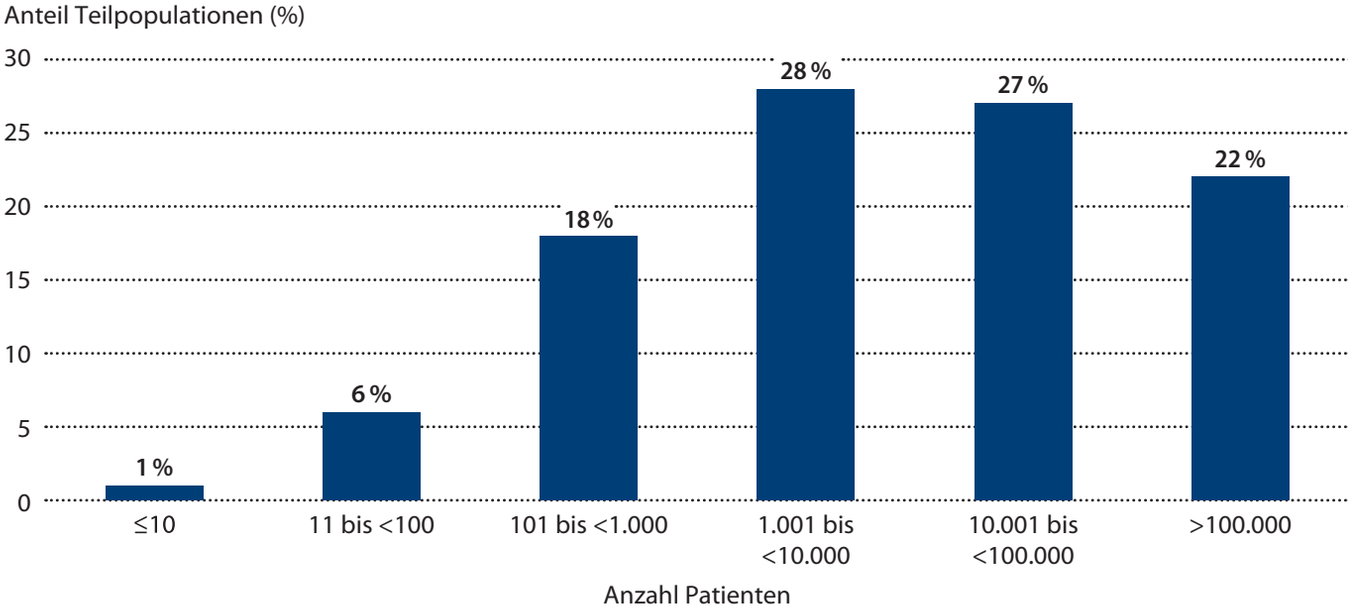
The starting point for mixed price is also often controversial, a lack of proven benefit in one subpopulation or another field of application. By the end of 2017, the G-BA decision reported such a result in 54 percent (n=123) of the subpopulations used for mixed pricing. This is particularly subject of controversy, if the result is not based on the available evidence, but on the lack of it. Thus, the finding „additional benefit not proven" does not imply that there is no additional benefit. By the end of 2017, an additional benefit was not proven on the basis of the available evidence in only in 16 percent (n=20) of the subpopulations used for mixed pricing. Far more often, study results were available, but the G-BA considered them inappropriate to answer the relevant questions.

2. Mixed price in daily medical practice

2.1 Are „real" prescription shares of active substances with mixed price understandable?

So far, the mixed price discussion is only theoretical and of legal nature. And weighting assumptions used for mixed pricing have not yet been empirically verified. At present, claims data of statutory health insurances provide the best available data source. It is questionable which subpopula-

Verteilung der vom G-BA geschätzten Prävalenz in den bislang differenzierten Teilpopulationen (n=441)



Quelle: Prof. Dr. Wolfgang Greiner, Julian Witte Lehrstuhl für Gesundheitsökonomie und Gesundheitsmanagement, Universität Bielefeld
Stand: 31.12.2017

Abbildung 2: In 25 Prozent der gebildeten Teilpopulationen beträgt die geschätzte Prävalenz weniger als 1.000 Patienten.

tions that have been defined by the G-BA for active substances with mixed price can be identified from the respective data. It should be interesting to check, whether the determined prescription shares of each subpopulation are identical with the estimated prevalence of the G-BA (where feasible).

For this purpose, the ability of depicting all subpopulations or fields of application as determined by the G-BA until 31 December 2016 for active substances with mixed price in the claims data of statutory health insurances was verified. Further fields of application following the initial evaluation were considered as well as new benefit assessments that might replace initial ones (where applicable). Such differentiation by

- demographic patient characteristics (age, gender),
- diagnostic criteria (clear differentiation of the diagnosis or severity using ICD-10) or by means of
- therapeutic criteria (previous and/or concomitant or combination therapy with ACT)

was required in order to trace back this information in the claims data of statutory health insurances. We selected a substance-related perspective. Therefore, not only one subpopulation must be identifiable as such in the claims data, but the field of application or all subdivided fields of application of a certain active substance must be clearly definable by the above mentioned criteria. Any fields of application that have been approved before or after the observational period were not considered. The table shows the number of subpopulations deviating from current procedure.

17 of a total 49 active substances with mixed price and 53 subpopulations were identified, for which quantification of subpopulation-specific prescription shares are at least theoretically possible on the basis of the mentioned criteria. Thus, the available active substance sample is limited. It is notable that only two of a total of 22 oncological substances with mixed price could be considered. This can be attributed to the fact that subpopulations for oncological substances are often differentiated by the patients' suitability for a certain alternative treatment (e.g. chemotherapy). However, diagnostic differentiation on the basis of the information contained in the claims data of statutory health insurances is not possible.

For almost half of the included active substances, selection of patients or allocation to a subpopulation, respectively, was performed as defined by the G-BA using the ICD-10-diagnosis code. This can refer to the differentiation of severity levels – as with aclinium bromide (Eklira Genuair®) – or on various oncology indications – as with ramucirumab (Cyramza®) (cf. Greiner, Witte 2018 for a detailed description of the methodology and associated limitations of the analysis).

2.2 Actual prescription shares of mixed prices in relation to the estimated prevalence by the G-BA

Based on prescription data of 2016, a high congruence can be identified between the actual prescription shares in the subpopulations and the prevalence as estimated by the G-BA for seven active substances with mixed price (cf Table 1). Individual subpopulations with or without proven benefit were evaluated separately but presented in summary.

For two active substances (dulaglutide and sitagliptin), there are several patients who can be allocated to multiple subpopulations within one year. For example, patients under dulaglutide treatment receive this pharmaceutical in combination with metformin and as a triple combination with two other oral antidiabetics within one year. An incremental treatment intensification might be one reason for this „change of subpopulation". In these cases, patients are assigned on the basis of the last subpopulation identified in the data set.

Realisierte Verordnungsanteile im Vergleich zur Prävalenzschätzung des G-BA bei Wirkstoffen mit Mischpreis*

Wirkstoff	Prävalenzanteile G-BA-Beschluss		VO-Anteile DAK-Gesundheit	
	ZN	Kein ZN	ZN	Kein ZN
Hohe Kongruenz				
Aclidiniumbromid	5 %	95 %	8 %	92 %
Axitinib	0,3 %	99,7 %	6 %[1]	94 %[1]
Sitagliptin	35 %	65 %	38 %[2]	62 %[2]
Edoxaban	81 %	19 %	89 %	11 %
Mepolizumab	80 %[3]	20 %[3]	76 %	24 %
Rilpivirin	99 %	1 %	100 %[1]	0 %[1]
Secukinumab	61 %	39 %	69 %	31 %
Mittlere Kongruenz				
Dulaglutid	30 %	70 %	44 %[2]	56 %[2]
Ramucirumab	15 %	85 %	33 %	67 %
Trametinib	Unbekannt		49 %	51 %
Niedrige Kongruenz				
Aclidiniumbromid/Formoterol	92 %	8 %	24 %	76 %
Emtricitabin, Rilpivirin, Tenofovir	3 %	97 %	52 %	48 %
Indacaterol/Glycopyrronium	92 %	8 %	23 %	77 %
Tiotropium/Olodaterol	92 %	8 %	51 %	49 %

[1] Daten basieren auf sehr kleiner Fallzahl (< 100 Patienten). [2] Es wurden Patienten identifiziert, welche innerhalb eines Jahres mehreren vom G-BA differenzierten Teilpopulationen zugeordnet werden können. Die Zuordnung erfolgte in diesen Fällen über die letzte Teilpopulation, in denen die Patienten identifiziert wurden. [3] Der G-BA gab im Rahmen der Nutzenbewertung von Mepolizumab keinen Schätzwert der Prävalenz in den zwei bewerteten Teilpopulationen an, sondern bezifferte lediglich eine Spanne. Die Schiedsstelle ging im Rahmen des Schiedsverfahrens jedoch von einer Verteilung 80/20 zugunsten der zusatznutzentragenden Teilpopulation aus. Entsprechende Angaben wurden hier als Prävalenzschätzung übernommen.

Quelle: Prof. Dr. Wolfgang Greiner, Julian Witte Lehrstuhl für Gesundheitsökonomie und Gesundheitsmanagement, Universität Bielefeld
*(n=16, basierend auf Daten der DAK-Gesundheit, Zeitraum: 01.01.2016–31.12.2016)

Tabelle 1: Für sieben Wirkstoffe lässt sich eine hohe Kongruenz zwischen VO-Anteilen und Prävalenzschätzung ermitteln.

In the mepolizumab procedure, the G-BA created two subpopulations depending on the co-medication. According to the G-BA decision, an additional benefit has not been proven for asthma patients who are not treated with oral corticosteroids or only in case of acute exacerbations. On the other hand, the G-BA saw an indication for a minor additional benefit for patients receiving oral corticosteroids regularly beyond treatment for acute exacerbations. Thus, classification of patients under mepolizumabe treatment can be made on the basis of simultaneous administration of mepolizumab with oral corticosteroids (ATC-Code R03BA). Any correlation of this co-medication with the incidence of acute exacerbations seemed to be impossible due to the lack of diagnostic accuracy. Therefore, „regular" administration of oral corticosteroids was alternatively defined as administration in three consecutive months. In the justification, the G-BA explicitly refers to an estimated prevalence and does not differentiate between the two subpopulations. Alternatively, the arbitration board's quantitative classification established within the scope of mixed pricing was taken (cf. Arbitration 130b-SSt. 2-17 dated 25 April 2017).

For two active substances (dulaglutide and ramucirumab), conditional congruence with the differentiated prevalence shares was observed as defined by the G-BA that was, however, lower than for the above mentioned active substances. For the active substance trametinib (Mekinist®), no clear statement can be made on the congruence of the realised prescription shares, as the G-BA does not specify prescription shares for the respective subpopulations (monotherapy, in combination with dabrafenib). Further information, e.g. from arbitration proceedings, is not available.

A low congruence of treated patients with the estimated prevalence as determined by the G-BA was observed in three of four of the evaluated active substances for the treatment of COPD as well as for Eviplera® (active substance: emtricitabine, rilpivirine, tenofovir disoproxil). For active substances used for the treatment of COPD, inaccuracies of inclusion criteria – ICD-10 classifies by level of severity in this indication analogous to the subpopulations of the G-BA, but this is not fully congruent – as well as potential diagnostic inaccuracies should be considered as a limiting factor. The observed incongruence with Eviplera® could be attributable to the fact that the approval was only extended by HIV patients with antiretroviral pre-treatment as a consequence of the mixed price two years after initial approval of the active substance; thus, there is still „catch-up potential" in this subindication.

For the active substances albiglutide (Eperzan®) and ocriplasmin (Jetrea®), a subpopulation-specific distribution of prescription shares was not indicated, as the number of cases was too low.

3. Potential solutions for the „mixed price dilemma"

In consideration of methodological limitations and limited samples, these analyses indicate only conditional congruence of the underlying assumptions of the mixed price and medical practice. However, the recent LSG decision challenges current practice. It remains to be seen how the BSG will decide on this issue. A legislative reaction is not expected in the meantime. If the BSG confirms the lack of legitimacy of mixed pricing, alternative approaches must be discussed. In current discussions, three approaches have emerged:

1. Partial exclusion of reimbursement
2. Indication-specific prices
3. Modifications of the „traditional mixed price".

3.1 Partial exclusion of reimbursement

With the decisions on the arbitration proceedings for albiglutide (Eperzan®) and idelalisib (Zydelig®), the LSG Berlin-Brandenburg indicated that reimbursement exclusions would be suitable to solve the mixed price issue (LSG Berlin-Brandenburg Ref. L 9 KR 213/16, Ref. L 9 KR 72/16 KL). The LSG also pointed out that the G-BA will not be able to solve the mixed price issue by means of exclusion of reimbursement alone, as the G-BA's Rule of Procedures (Chapter 4, § 5) require a hearing procedure to be held before a decision about potential reimbursement exclusions or therapeutic advices can be issued. This would preclude a simultaneous decision-making about the result of benefit assessment and determination of exclusion of reimbursement. In any case, the way prices are determined moves away from the initial AMNOG idea of ensuring that innovative pharmaceuticals should be available for prescription in a timely manner (BT-Drs. 17/2413, p. 1).

Moreover, it should be considered that the result of benefit assessment is based on an average on the basis of a selected patient cohort of clinical studies. However, for prescription in the statutory health insurance system, other patient-related aspects play a role (e.g. contraindications or compliance-promoting aspects) upon selection of a certain therapeutic alternative beyond the formal „additional benefit". Hence, also new pharmaceuticals for which an additional benefit has not (yet) been proven and particularly those with a mixed price can gain therapeutic significance (cf. Greiner, Witte 2017, S. 160; GKV-Spitzenverband 2017). In case of a mandatory exclusion of reimbursement for the respective subindications these prescriptions would at least partly be at issue.

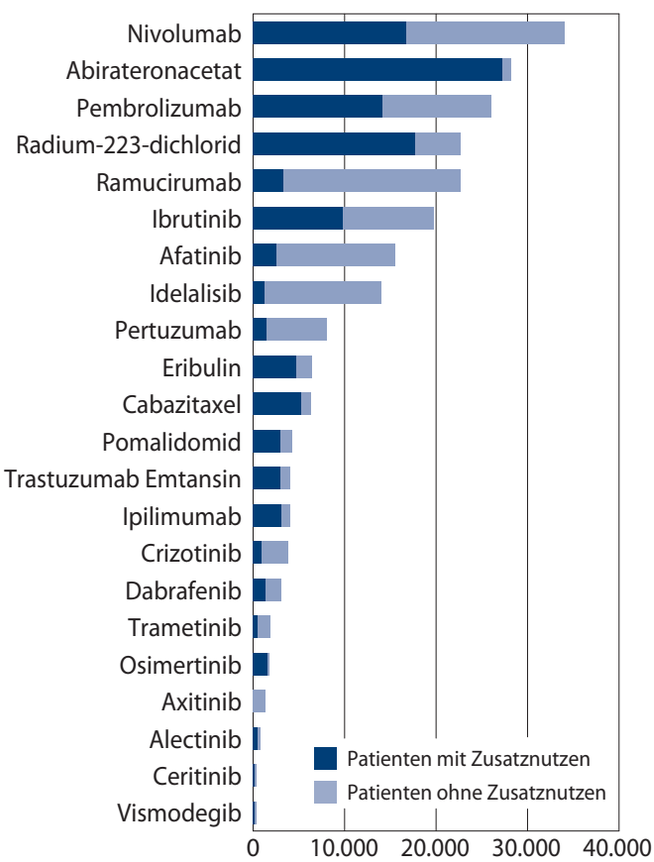
The consequences for prescription can be illustrated using the example of new oncology products: A mixed price was negotiated due to the fact that an additional benefit was partly proven for 22 of 54 oncology products that underwent benefit assessment by the end of 2017. Excluding the subsections of application without proven additional benefit from prescription, would mean that these 22 products are no longer be available for 48 percent of the patients who might be suitable candidates in the respective application areas (cf. Figure 3).

However, selective exclusions of reimbursement are not „new" and have already been incorporated in the SGB V. Mid 2016, the G-BA issued exclusions of reimbursement for the PCSK9 inhibitors alirocumab (Praluent®) and evolucumab (Repatha®) for subsections without additional benefit according to Section 92 Paragraph 1 SGB V before the LSG decided on albiglutide. A mixed price could thus be avoided which might have resulted in a market withdrawal due to the small proportion of this patient population and the efficient ACT. Therefore, selective exclusions from partial reimbursement upon request or in agreement with the pharmaceutical company seem to be one justifiable and feasible instrument among others, but should only be the solution of choice in very few constellations due to their far-reaching consequences for prescription – both from the industry's perspective and for reasons of patient care.

3.2 Indication-specific prices

Indication-specific prices could be another solution for the mixed price issue. In the USA, such a model was already proposed in 2014 to determine the value of a pharmaceutical across several indications or subgroups (Bach 2014). In Germany, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) suggested benefit-oriented pricing for the respective application area in 2016, the so-called „benefit-oriented reimbursement" (NoE, nutzenorientierte Erstattung) (Haas et al. 2016). The concept was developed to negotiate a different reimburse-

Teilpopulation mit und ohne Zusatznutzen neuer Onkologika unter Mischpreis



Quelle: Prof. Dr. Wolfgang Greiner, Julian Witte Lehrstuhl für Gesundheitsökonomie und Gesundheitsmanagement, Universität Bielefeld; Stand: 31.12.2017

Abbildung 3: Für 48 Prozent der potenziell in Frage kommenden Patienten stünden die 22 Onkologika mit Mischpreis nicht mehr zur Verfügung.

ment amount for every subpopulation. A base price that is aligned with the ACT forms the basis.For a proven benefit in one subindication a surcharge applies. Moreover, the model specifies certain exclusion criteria.

The heart of an indication-specific pricing is the allocation and documentation of prescriptions in accordance with the subpopulations as specified by the G-BA. This is also associated with potential disadvantages:

- High encoding or documentation requirements
- High funding requirements
- Susceptibility to manipulation
- Lack of flexibility for individual cases.

Indication-specific prices would solve the issue of lacking economic efficiency, as they would turn a feasible prescription in individual cases to a prescription that is not only feasible but also economical in individual cases (because another price is used). However, within the framework of the model of indication-specific pricing, a comprehensive encoding system should be introduced for all subpopulations according to the G-BA decision. This would be possible with the current infrastructure that has been developed for the PIS. However, additional encoding would not only be associated with a significant additional expenditure of time for physicians – which might not contribute to an increase acceptance of a PIS aimed at providing information (cf. Ärzte Zeitung 2016), but might also be susceptible to errors and not strategy-proof („up and right coding").

In exceptional cases, indication-specific pricing is already possible and was realised for certain AMNOG pharmaceuticals (e.g. for cabozantinib). This is possible because of separate reimbursement amounts for products with the same active substance distributed under different trade names with different fields of application. The legislator included a hardship clause in Section 130b Paragraph 3a SGB V to allow for stipulation of different reimbursement amounts, if the same reimbursement amount would be inappropriate with regard to prescription or would constitute undue hardship.

3.3 Modification of the „traditional mixed price"

In the third option, the mixed price is maintained as a uniform reimbursement amount for certain subsets. In principle, two different models could be developed:

1. „Ex ante model" using price-quantity agreements

2. „Ex post model" using realised volume shares on the basis of physician samples.

Both models have in common that legal clarification about mixed pricing and the associated efficiency of the reimbursement amount would be required, but it should better be aligned with the actual healthcare system.

Price- volume agreements

According to the National Association of Statutory Health Insurance Funds (GKV-SV), every contract under Section 130b SGB V that was concluded after the AM-VSG came into force, already contains a provision about quantity-related aspects (BT-Drs. 19/916, p. 12). Specification of the current mixed price system by means of a mandatory scaling of the reimbursement amount aligned with the prescription volumes that have been realised in the market constitutes a fair balance of the interests of both industry and paying parties with comparatively reasonable transaction fees and rapid implementation. In case of a mandatory linking of reimbursement amount to (predicted) sales volume, drastic price reductions should be agreed for subsequent prescriptions, if the predefined threshold is exceeded. Thus, a reduction of the reimbursement amount to 0 Euro or an amount that does not result in higher annual treatment costs as compared to the ACT would be possible. Other models, e.g. incremental price reduction for increasing prescription volumes are feasible and have been established on an international basis (Messori 2016).

In theory, this principle presents several advantages: Predictable prices and volumes (for paying parties), guaranteed minimum turnover – given an adequate market penetration – as well as a reduction of market penetration obstacles (for the pharmaceutical company). However, from the viewpoint of the GKV-SV, there are three main reasons against price-volume agreements:

- Concealment of the actual reimbursement amount,
- Lack of transparency of the reimbursement amount for the physician at the time of prescription,
- Additional bureaucratic costs of reverse transaction via routine data from statutory health insurances (V. Stackelberg et al. 2017, p. 173).

From the GKV-SV's perspective, both contractual content (volume-related pricing, prescription volume limits) and the time when volumes exceeded the agreed values shall be published for the practical implementation of a price volume agreement (see ibid). This is neither required for the execution of price agreement-based prescription quantities, nor for the representation of subindications in routine data from statutory health insurances, as this is a bilateral agreement between GKV-SV as (price) demander and the pharmaceutical company as provider which is only settled on this level.

Ex post model using a physician sample For an ex post solution of the problem of a prescription-based volume weighting, actual prescription data must be collected representing the prescription shares of a pharmaceutical in the subpopulation that underwent benefit assessment. Based on this data, a mixed price could be adjusted by subsequent reimbursement to achieve a benefit-oriented reimbursement amount according to Section 130b SGB V. All relevant information must be documented or encoded by the physician to guarantee traceability. The model of indication-specific pricing also includes encoding or benefit-oriented reimbursement with all mentioned disadvantages.

In principle, it would also be possible to collect the actual volumes that are required for subsequent settlement of a mixed price using a physician sample. In contrast to a „total market solution" this would present several advantages (reduced costs, higher speed, flexibility, and accuracy). To achieve this, it is essential that the sampling methodology ensures the highest standards.

This is particularly applicable to the statistically appropriate size and representation of the sample. Therefore, determinants for the measurement of representation would have to be predefined, e.g. prescription volume for pharmaceuticals with reimbursement according to Section 130b, specialist field or region of the prescriber. In addition, the quality of sample data would have to be monitored regularly and evaluated independently.

4. Summary

In the absence of proper legislation, the universal and cross-procedural mixed price is in principle a suitable interim solution to establish a benefit-oriented reimbursement amount and remains common practice even after the LSG decision. No short-term changes are to be expected, as all previously discussed mixed price alternatives require further specification in the SGB V by the legislator.

They are associated with several advantages and disadvantages that should be carefully weighed. Price-volume agreements for a continuous adjustment of the mixed price seem to be the easiest and fastest option. The required instruments are already available in the SGB V and only have to be slightly modified. However, if the legislator does decide to link the individual price components of the mixed price to actual prescription volumes in the respective subsections of an application, the introduction of the PIS should not be combined with a documentation or encoding obligation for AMNOG subpopulations for all physicians. With the collection of these data in a representative sample, prescription-oriented mixed pricing could be realised faster, cheaper and thus more precisely.

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Ten theses on fair pricing for inconsistent decisions on the additional benefit

Professor Jürgen Wasem | Chair of the Arbitration Board according to Section 130b SGB V

Prescription is normally considered economical in terms of an underlying mixed price, if it is apropriate in the individual case and if prescription shares correspond to those used for the calculation of the mixed price. The mixed price should be adjusted, if the prescription shares that are used as a calculation base are not realised in the actual medical care situation. To facilitate working, the arbitration board requires all relevant data.

Inconsistent benefit assessment decisions for a pharmaceutical with several patient groups or indications, respectively, for which (early) benefit assessment according to Section 35a SGB V by the Federal Joint Committee (G-BA) produced different outcomes regarding the extent of the additional benefit as compared to the appropriate comparative treatment (ACT) defined by the G-BA, are a common phenomenon.

This issue must be addressed during price negotiations according to Section 130b SGB V. It has become common practice to refer to a so-called „mixed price", if the agreed reimbursement amount takes the heterogeneity of the benefit assessment decision into consideration. Typically, (fictional) partial reimbursement amounts are initially determined for the individual patient groups or indications, respectively, that are then weighed and combined to a uniform reimbursement amount.

If the G-BA granted an additional benefit to a pharmaceutical in all patient groups or indications, but the extent of the additional benefit varies, this is often referred to as a „small" mixed price; in this article, we will use this term, too. In contrast, the term „large" mixed price is used, if an additional benefit has not been granted for at least one patient group, while an additional benefit has been granted by the G-BA for at least one other patient group.

The determination of a reimbursement amount in cases with inconsistent benefit assessment decisions is demanding. This has been the case since the introduction of the German Pharmaceutical Market Reorganisation Act (AMNOG) in 2010, and has become more accentuated since the Berlin-Brandenburg Superior State Social Court has questioned the legitimacy of agreeing at least „large" mixed prices in 2017. Against this background, the following ten theses have been formulated: They primarily represent my perspective as health economist who has been

engaged in topics around control of the pharmaceutical market for many years as well as experiences as Chair of the Arbitration Beard according to Section 130b Paragraph 5 SGB V in the context of my task to determine reimbursement amounts.

Thesis 1

The contractual partners of reimbursement agreements according to Section 130b SGB V, i.e. National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and the pharmaceutical company that placed the pharmaceutical with the new active agent on the German market, are in fact not faced with a legal dilemma, if there is a consensus that a mixed price shall be agreed upon. This also applies for the arbitration board, if it comes to an agreement (with or without arbitration award). The LSG Berlin-Brandenburg also confirmed this position.

And where there's no claimant, there is no Superior State Social Court. However, the situation is of course somewhat problematical: Both sides and the arbitration board are bound by law and statute even in case of a consensus. If mixed prices are in fact illegal, they must not be agreed upon – not even by means of consensual agreements. Thus, this issue does not only apply for these few cases requiring arbitration, but for almost one third of all pharmaceuticals with new active substance launched on the German market.

Thesis 2

There are alternative scenarios to the mixed price, such as indication-specific prices in combination with partial exclusion of reimbursement – both of which present several advantages and disadvantages. However, if politics does not adapt these alternative approaches, there is usually no alternative in case of inconsistent benefit assessment decisions. I would, in fact, appreciate a rapid clarification by the legislator on this matter. An appeal on the relevant decisions was permitted by the LSG Berlin-Brandenburg and the arbitration board appealed. Consequently, the Federal Social Court (BSG) will have to deal with this topic and will obviously take a decision in the course of 2018.

Prescription is normally considered economical, if it is appropriate in the individual case and if mixed price and prescription shares correspond to those used for the calculation of the mixed price.

In case the BSG confirms the findings of the LSG Berlin-Brandenburg regarding incompatibility with applicable law, it would then be politics' turn to change the legal basis in due time. Otherwise, legally binding reimbursement

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amounts can no longer be determined in case of inconsistent benefit assessment decisions. However, I would prefer not to wait for legal clarification by the Federal Social Court.

Thesis 3

Since mixed prices are determined on federal level, there has been major debate about their efficiency. Some regional Associations of Statutory Health Insurance Physicians and statutory health insurances propagate that prescription of a pharmaceutical with mixed price for the indication or patient group without additional benefit as determined by the G-BA is uneconomical[1]. My opinion is that this conclusion is wrong. From my point of view, the following applies: Prescription is normally considered economical, if it is appropriate in the individual case and if mixed price and prescription shares correspond to those used for the calculation of the mixed price. The mixed price should be adjusted, if prescription shares used as a calculation base are not realised in the actual medical care situation. I therefore propose that the contractual partners of the framework agreement under Section 130b SGB V (National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and associations of the pharmaceutical industry) integrate this update into the framework agreement and issue appropriate regulations.

Thesis 4

The statement of Thesis 3 also applies for reimbursement amounts that have been determined by the arbitration board. Upon calculation of the mixed price, the arbitration board must represent the expected medical care situation (indication shares) as closely as possible. In many cases, this does not correspond with the prescription shares in the G-BA decision on the benefit assessment, as these shares are based on different assumptions („What would the proportion of patients be, if the pharmaceutical would cover 100 per cent of the market?"). If jurisdiction excludes deviations from the G-BA decision, the legislator should also readjust and correct the inappropriate jurisdiction. However, we need a procedure to make a best guess of the prescription shares in individual indications or patient groups, respectively. As mentioned, in my opinion framework agreements would be a suitable option.

Thesis 5

From my point of view, it would also be legitimate, if the arbitration board takes a (majority) decision without stipulating a mixed price, but a (non-mixed) reimbursement amount for indications with additional benefit indicating that this price does not cover indications without additional benefit. This is one possible implementation of the LSG decision, as the LSG points out that one problem was that the reimbursement amount was too low for indications with additional benefit. With this approach, this would no longer be the case. One consequence is that prescription of this pharmaceutical in an indication without additional benefit would be considered uneconomical; however, this would not be an issue of the arbitration board.

Thesis 6

A typical constellation for mixed prices are indication extensions – e.g. if the G-BA determined an additional benefit during the first approval of a pharmaceutical, but decided that an additional benefit is not proven for a subsequent indication. If the arbitration board shall take reasonably consistent decisions, it must be informed about fictional indication-specific partial reimbursement amounts for previous indications as well as potential ACTs that underwent additional benefit assessment[2]. It therefore appe-

ars necessary to grant the pharmaceutical company the right for exclusion from partial reimbursement for indications for which the G-BA has not granted an additional benefit (upon request).

It appears inappropriate that pharmaceutical companies must distribute a certain pharmaceutical in an uneconomical indication. However, removing it from the market would neither be a good option nor would it be feasible for reasons of patient care due to the additional benefit in other indications[3]. Again, the legislator should make adjustments, as current law does not provide basis for exclusion from partial reimbursement.

However, we need a procedure to make a best guess of the prescription shares in individual indications or patient groups, respectively.

Thesis 7

In case of inconsistent benefit assessment decisions, the arbitration board only considered European reference prices and annual treatment costs of comparable pharmaceuticals only for indications or patient groups with additional benefit, respectively, for the determination of a „large" mixed price. Whereas in indications or patient groups without additional benefit, it used the annual treatment costs of the ACT as a basis for the mixed price. Whether this approach is legally binding, can be discussed controversially, at least pharmaceutical companies stress the fact that we deal with a pharmaceutical „with" additional benefit and not „without" additional benefit. Irrespective of whether the current practice of the arbitration board is legally binding or not, the question arises as to whether the arbitration board's practice over the past six years has become a legally effective self-commitment over time.

Thesis 8

With the Act on Strengthening Pharmaceutical Supply in Statutory Health Insurance (AMVSG), the legislator changed the provision that in cases where an additional benefit has not been proven, the annual treatment costs of the respective pharmaceutical must not be higher than the annual treatment costs of the most economic ACT to a „directory" provision. In my opinion, this mandatory provision can be used as a basis if a „large" mixed price is determined as outlined in Thesis 7 for the determination of a partial reimbursement amount without additional benefit.

For example, a certain pharmaceutical could be indispensable for a certain indication, although an additional benefit has not been proven in this indication. This could be a potential criterion for the arbitration board to consider higher annual treatment costs as compared to the most economic ACT in the determination of a partial reimbursement amount for this indication. As a result, the amount exceeding the annual treatment costs of the ACT in that indication would be considered in the reimbursement amount.

Thesis 9

In my opinion, the question raised by the LSG Berlin-Brandenburg about the required depth of justification in the monetisation of the additional benefit is more relevant than the mixed price issue. With the introduction and further development of AMNOG, the legislator was well aware that the arbitration board must continue negotiations of the contractual partners according to Section 130b SGB V with the goal to reach an agreement and take a majority decision in case of conflict. Although the arbitration board must be internally consistent, less stringent requirements of the obligation to state reasons may be applied[4]. The legislator was well aware what he was doing when he formu-

lated: „The arbitration board takes a decision upon the free assessment of all circumstances in the individual case considering all peculiarities of the respective therapeutic area."

Thesis 10

It is necessary to distinguish between the arbitration award's depth of justification and transparency of the underlying calculation. In this point, I agree with the LSG Berlin-Brandenburg that transparency was certainly rather neglected in the past. Since the LSG decisions, the arbitration board has thus increased transparency about their calculation in the recital section of the arbitration award significantly.

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Subgroup evaluation: Challenges for pricing and care

Birgit Fischer, Dr Jan Bungenstock, Dr Andrej Rasch | Association of Research-Based Pharmaceutical Companies (vfa)

According to the Berlin-Brandenburg Superior State Social Court (LSG), there is no sufficient legal basis for mixed prices as determined by the AMNOG Arbitration Board. This puts increased pressure on physicians to refrain from prescribing new pharmaceuticals for many patient groups. However, general partial reimbursement exclusions are not a suitable instrument to deal with subgroup evaluations by the G-BA. Subgroup-based reimbursement is also an unsatisfactory solution for the reimbursement of pharmaceuticals with several subgroups as defined by the G-BA. The AMNOG mixed price is not part of a problem, but the solution for the determination of prices while ensuring and maintaining a high quality level of medical care. Therefore, a solid legal foundation has to be established. Moreover, a well-organised knowledge transfer can contribute to an increased quality of medical care. However, prescription control via a physician information system is associated with a significantly reduced quality of patient care.

Introduction

On 28 June 2017, the Berlin-Brandenburg Superior State Social Court (LSG) has decided within the scope of two legal proceedings that there is no sufficient legal basis for mixed prices as determined by the AMNOG Arbitration Board[1]. This puts increased pressure on physicians to refrain from prescribing new pharmaceuticals for which a reimbursement amount has been specified in many patient groups (i.e. patients according to the subgroups as defined by the G-BA): In these areas, physicians are cautioned against using pharmaceuticals in patient groups for which the Federal Joint Committee (G-BA) has not granted an additional benefit[2].

The factual LSG's interpretation is, however, incomprehensible. It challenges the whole AMNOG procedure of price determination for new pharmaceuticals we have used for the past seven years although AMNOG mixed pricing is not an invention of the pharmaceutical industry. While AMNOG could initially be understood in that negotiations are only conducted on the basis of a merely „binary" decision on the additional benefit of the respective pharmaceutical (yes/no), shortly after the law came into force statutory health insurances understood AMNOG mixed pricing as a purposeful specification of AMNOG's legal framework for pharmaceuticals with several patient groups and handled accordingly since 2013. On closer examination it becomes apparent that the current AMNOG practice of mixed pricing is superior to the other two alternatives.

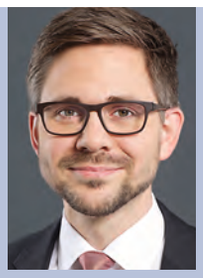
The purpose of this article is to demonstrate that – from a medical point of view – general partial reimbursement exclusion are not suitable to deal with subgroup evaluations by the G-BA when it comes to pricing and provision of medical care (Chapter 2.1). Moreover, we will illustrate that subgroup-based reimbursement is also an inferior solution

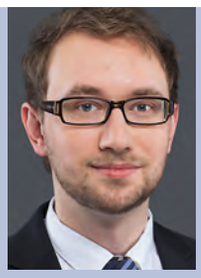
for the reimbursement of pharmaceuticals with several subgroups as defined by the G-BA (Chapter 2.2). Against this background, we will show in Chapter 2.3 that the AMNOG mixed price which has been challenged by the LSG but proven itself in practice is not part of a problem, but the solution that needs to be reinforced by legislation. In this context, we will also answer the question why a physician information system must not control medical prescription, but only provide information to facilitate medical decision-making (Chapter 3).

2. Three types of reimbursement for subgroup evaluations

There are only three options to handle subgroup evaluations by the G-BA when it comes to pricing and provision of medical care (Figure 1):

- One average price for a pharmaceutical („mixed price") to ensure economic prescription in all subgroups.
- Partial exclusion of reimbursement restricting medical care for patients with equivalent therapy alternatives for which the G-BA does not see an additional benefit.
- Subgroup-based reimbursement, i.e. the reimburse-





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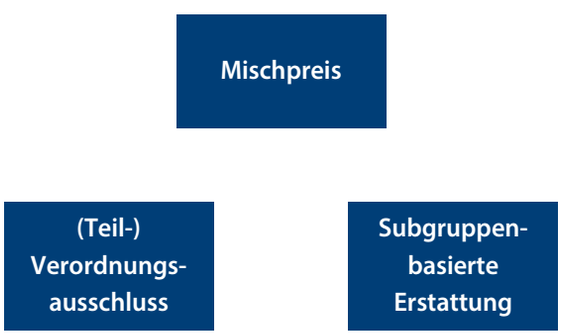
Subgruppen in der Erstattung: Wir müssen uns für eine von drei Alternativen entscheiden



Quelle: Eigene Darstellung

Abbildung 1: Generell sind nur drei Arten der Erstattung von Subgruppenbewertungen möglich.

ment amount does not depend on an average additional benefit of a pharmaceutical, but includes several reimbursement amounts on the basis of the additional benefit of various subgroups.

For these three alternatives, the following applies: We have to take a decision. Pharmaceutical companies need planning reliability and AMNOG has to remain practicable. The present situation of uncertainty for all stakeholders needs clarification. Therefore, the legislator has the urgent task of establishing a solid legal basis for the common practice of mixed pricing.

2.1. General partial reimbursement exclusions are irresponsible from a medical point of view

Given the missing legal basis of mixed prices as determined by the LSG, prescriptions in patient groups with non-proven additional benefit can be sanctioned or the use of mixed price pharmaceuticals excluded for certain patient groups, respectively. However, this alleged way out is not an appropriate solution[4]. And despite reports to the contrary, this issue is not relating to individual cases.

AMNOG pharmaceuticals typically have several patient groups: 59 percent of all pharmaceuticals in AMNOG fall in this category. According to the G-BA, 41 percent of these pharmaceuticals only have an additional benefit in selected patient groups. Should the G-BA decide to exclude patient groups with non-proven additional benefit as a consequence of the LSG decision, treatment with innovative pharmaceuticals would be at stake for the respective pharmaceuticals. These pharmaceuticals deemed necessary and appropriate by physicians would then no longer be accessible for some 38 percent of all patients[5]. But what does „additional benefit not proven" really mean?

It was, in fact, not AMNOG's purpose to have a negative impact on the patient's reimbursement claim. AMNOG rather aims at determining the correct reimbursement amount or price of pharmaceuticals, respectively. If a pharmaceutical fails to prove its superiority against the appropriate comparative treatment (ACT) as determined by the G-BA at the time of the evaluation, the law provides that it shall not be more expensive than the ACT[6]. These pharmaceuticals shall, however, remain available, as they have at least an equivalent benefit as the ACT as defined by the G-BA. In fact, therapeutically equivalent alternatives are required, especially because patients are different. And the following principle does still apply: The absence of evidence is not an evidence of absence.

The decision „additional benefit not proven" is not uncommon in the AMNOG procedure either. So far, the G-BA has not granted an additional benefit in 41 percent of all pharmaceuticals. Meanwhile, many new pharmaceuticals are prescribed for which the G-BA has not granted an addi-

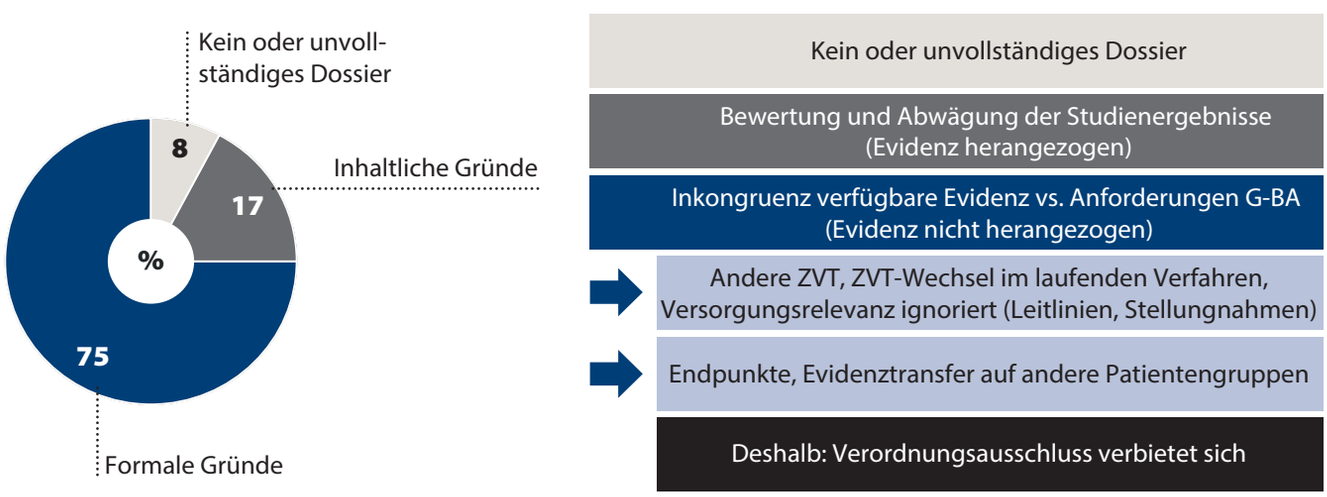
tional benefit in general or for subindications: 62 percent of all patients in the subgroups defined by the G-BA are treated with pharmaceuticals that have an equivalent benefit as the ACT as defined by the G-BA[7].

This basic principle of AMNOG – i.e. preservation of therapeutically equivalent alternatives – serves the quality of medical care in Germany as confirmed by current treatment guidelines of scientific medical associations. According to the professional associations, many pharmaceuticals for which the G-BA has not determined an additional benefit, do provide a significant patient benefit and thus play a significant role in the healthcare landscape. Hence, treatment guidelines recommend these drugs as a valuable therapeutic alternative or even as treatment without alternative. Therefore, the term „non-proven additional benefit" does not necessarily mean that there is no additional benefit[8].

It would be irresponsible to discriminate pharmaceuticals without additional benefit according to the G-BA as „bad pharmaceuticals" and redesign AMNOG in such a way as to restrict prescribability of those pharmaceuticals thus denying patients access to them. This would mean cutting back valuable therapeutic alternatives or providing therapies without any alternative which would in turn reduce both standard and quality of medical care.

In no other area of healthcare, the starting point for evaluations is as good as it is in the pharmaceutical sector: For every new pharmaceutical a reliable database is available from the approval procedure about both the benefit and potential risks of treatment. However, in many cases the

Ausschlaggebende Gründe für einen G-BA-Beschluss „Zusatznutzen nicht belegt"



Quelle: Eigene Darstellung

Abbildung 2: In drei von vier Fällen wird die Bewertung „Zusatznutzen nicht belegt" aus formalen Gründen gefällt.

G-BA does not consider these findings in their assessment.

Analysis of the current practice shows: 51 percent of all studies provided by manufacturers are not at all taken into consideration by the G-BA. In many cases, no approval studies have been conducted on the ACT as determined by the G-BA so that the G-BA considered them not relevant per se or the G-BA changed determinations for the ACT during the benefit assessment procedure. The contents of other valuable evidence that does not exactly comply with the ideal requirements of the G-BA are often not evaluated at all (endpoints, evidence transfer to other patient groups). As a result, in 75 percent of all cases, formal reasons are a major factor for the decision „additional benefit not proven" – and not the G-BA's evaluation of the study contents (see Figure 2)[9].

Particularly for the treatment of children and adolescents, partial reimbursement exclusions would have drastic effects, as e.g. an evidence transfer during the approval is not recognised by the G-BA. In daily practice, physicians might be faced with the challenge that a certain HIV drug that is approved for the treatment of adults and children over six years, will no longer be reimbursed for treatment in children and adolescents, because the G-BA has not granted an additional benefit in this subpopulation for formal reasons. Under these circumstances, the strategy of partial reimbursement exclusion as outlined by the LSG should definitely not be pursued.

2.2. Subgroup-based reimbursement will provoke manipulations by health insurances

For some time now, health insurances have been promoting subgroup-based reimbursement. Reimbursement amounts shall no longer be determined in accordance with the current AMNOG practice, i.e. based on the average additional benefit of a pharmaceutical, but various reimbursement amounts shall be determined for every subgroup depending on their additional benefit.

Like partial reimbursement exclusions, the idea of various prices for one pharmaceutical for different patient groups is associated with major disadvantages for medical care[10]. This is due to a very similar circumstance, as we already know it from the current discussion about the self-interest of health insurances in connection with the morbidity-oriented risk adjustment scheme (Morbi-RSA)[11]: By providing patient groups in routine data, health insurances would be extremely encouraged to advise physicians about encoding for reimbursement purposes according to their own interests. As a result, they would have direct control over medical prescription. Physicians would only be promised „freedom of recourse", if they adopted the „right" encoding and prescription behaviour from the health insurances' perspective.

Moreover, it should be remembered that the extent of subgrouping constitutes a special path as compared to international standards. While subgrouping is an exception in France, it is common practice in Germany[12]. It should also be noted that the statistical evidence alone and thus the probability to demonstrate an additional benefit in the subgroups that have been determined by the G-BA, declines with the number of subgroups. It becomes quite attractive for the G-BA to create as many subgroups as possible, particularly in case of subgroup-based reimbursement, as thereby as many patient groups – for which the pharmaceutical might be suitable – as possible receive the lowest possible patient group-specific reimbursement (for these patient groups). Emphasis will then rather be on the price than on medical evidence.

Similar to the above mentioned inappropriate behaviour of health insurances regarding Morbi-RSA, subgroup-based reimbursement would thus bear considerable manipu-

lation risks due to the necessity of encoding by physicians and communication to health insurances: For economic reasons, physicians would be encouraged to consistently encode patient groups for which the G-BA has not proven an additional benefit ensuring that the pharmaceutical company gets the lowest possible patient group-specific reimbursement amount. This has only one ultimate objective: To have an influence on medical treatment decisions by directly controlling medical prescriptions – at the expense of medical care. Physicians might become intrinsically motivated to choose the wrong, but cost-efficient encoding only for reasons of economy.

According to the ideas of the health insurances, patient group-specific reimbursement amounts and especially the base price that is often based on generic treatment costs are listed publicly and settled by means of trade levels. This will aggravate the existing problem of international price referencing for manufacturers. Due to the very low public prices for patient groups for which the G-BA has not proven an additional benefit it is even more likely that they will be forced to remove certain pharmaceuticals from the German market.

Moreover, such a public listing at the low base price would cause a boom in the parallel export business. Since the beginning of AMNOG, export registrations for AMNOG products by parallel traders at the European Medicines Agency (EMA) have increased13. In a system of subgroup-based reimbursement amounts, distributors can purchase these pharmaceuticals at the lowest base prices from German pharmacies or wholesalers and sell them at higher prices in other European countries. The business model of profit-oriented transport of pharmaceuticals that have been produced for German patients into other European countries might be even more profitable as is already the case today. Those who have to suffer the effects in the end are patients whose pharmaceuticals would no longer be available in sufficient quantities in Germany due to supply bottlenecks caused by parallel export.

The current mixed pricing approach is ultimately nothing else than a pragmatic yet effective and simple combination of patient group-specific prices into one reimbursement amount. Moreover, this approach of having one price for a pharmaceutical is in accordance with social and pharmaceutical legislation. Moving away from this principle will just raise new questions.

2.3. The mixed price is the solution and not the problem

It is based on a mixed calculation: In reference to the various levels of evidence for additional benefit for various patient groups, a mixed price is negotiated in due consideration of the costs of the appropriate comparative treatment and the number of patients. The AMNOG framework agreement provides that arrangements are made for the event of deviations from the expected patient numbers.

Negotiation of a mixed price creates a balance between both contractual partners: The pharmaceutical company agrees to an average price for a patient group with additional benefit as determined by the G-BA. At the same time, health insurances agree to an average price for a patient group without additional benefit as determined by the G-BA. An economic prescription in all patient groups is thus ensured nationwide[14]. AMNOG also provides that the negotiating partners themselves can decide about specific arrangements for patient numbers and potential deviations, as changes of prescription shares can arise for different reasons.[15].

In this context, health insurances have long pointed out that the consideration of patient numbers is already part of AMNOG[16]. Suddenly, however – after seven years of

mixed pricing – health insurances request more differentiated encoding specifications for physicians for the AMNOG mixed price alone. „Coincidentally", this request corresponds to the health insurances' own idea of a physician information system, i.e. regular documentation of the relevant patient group for the health insurance and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).

This claim is incomprehensible: The GKV-Spitzenverband already has diagnostic data according to Section 217f. in combination with Section 295 SGB V. Moreover, data on the prevalence are provided in the G-BA decision and can use other public and private data sources to quantify patient group-specific morbidities for the determination of an appropriate AMNOG mixed price. The agreed and expected prescription share, respectively, that has been negotiated according to AMNOG regulations can already be reviewed within the scope of accounting with health insurances according to Section 300 SGB V. Therefore, the demand currently raised by health insurances can only be explained by the fact that also becomes apparent in connection with the physician information system and the idea of subgroup-based reimbursement, i.e. to have direct control over the physicians' prescription behaviour and thus restrict medical care.

So far, AMNOG mixed pricing worked very well in practice on the basis of the available data. It should thus be clearly defined at legal level to establish legal certainty for prescribing physicians in light of the LSG decision of summer 2017. In fact, additional encoding demands for physicians are not required: Unlike the case with patient group-specific reimbursement amount, neither the technically and administratively time-consuming and manipulable direct encoding of medical prescriptions nor communication to the health insurances resulting in direct prescription control are required.

Particularly because AMNOG-contractual partners can already easily obtain morbidity information from third parties, new encoding specifications are not required for mixed pricing. They would in turn encourage health insurances for example to submit diagnostic proposals and provide encoding advice as in the case of Morbi-RSA that have recently been prohibited with the Act on Therapeutic Products and Medical Aids (HHVG).

2.4. Preliminary conclusion: It's the legislator's turn

Consequently, a closer look reveals the clear advantage of the mixed price concept as compared to partial reimbursement exclusions suggested by the LSG or the interest-based idea of health insurances, i.e. subgroup-based reimbursement (Figure 3)[17]. The mixed price is daily common practice, it is practicable and pragmatical and ensures economic treatment for all patient groups without the necessity of encoding prescriptions, whereas partial reimbursement exclusions would be irresponsible from a medical point of view. G-BA decisions are not individual treatment recommendations and thus not suitable for prescription control. Subgroup-based reimbursement is associated with direct control of physicians. This involves prescription control by health insurances and carries a high manipulation risk. Moreover, it provokes supply bottlenecks caused by parallel export.

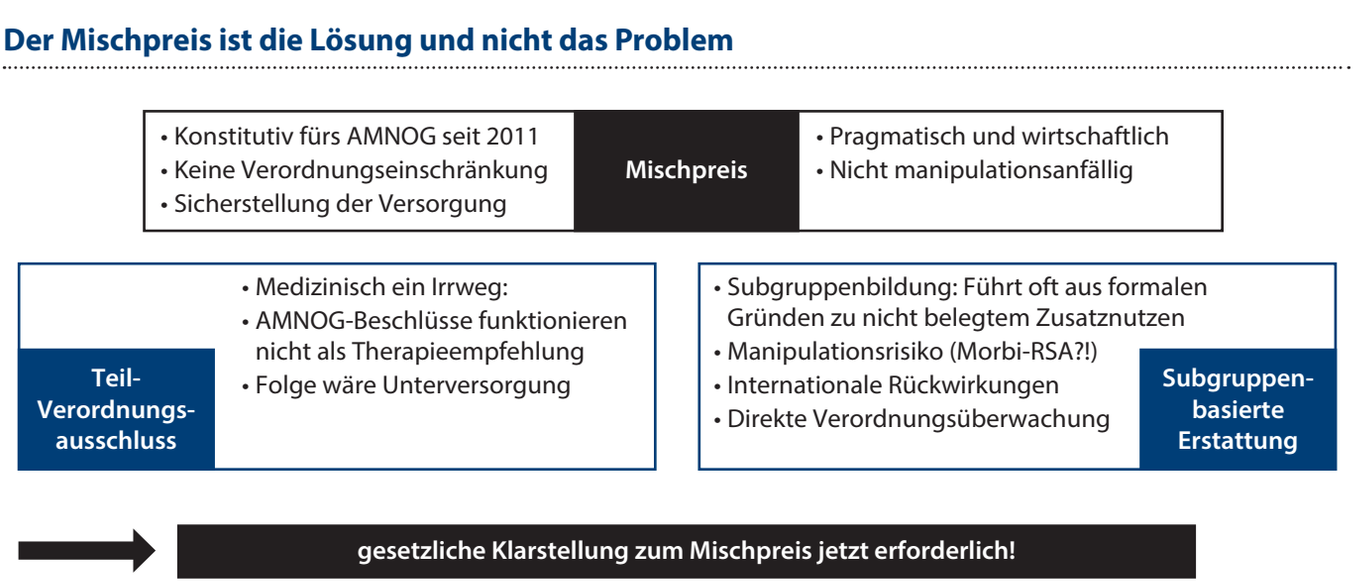
So far, there weren't any dissenting voices or demands for legal clarification of the AMNOG mixed price from the GKV-Spitzenverband. This is not surprising. In view of the present uncertain legal situation, it has a wider scope for action as compared to the negotiation partners of the pharmaceutical industry. On the one hand, there are constellations in which the GKV-Spitzenverband can agree on a mixed price with the pharmaceutical company. On the other hand, the GKV-Spitzenverband may object to a mixed

price in individual cases with reference to the LSG decision and does not have to be afraid of a mixed price before the arbitration board.

Thus, it's the legislator's turn now. Negotiating partners need a sufficient and equally wide range for the determination of the appropriate reimbursement amount for AMNOG pharmaceuticals with several patient groups. This article clearly illustrated the advantages of using the proven approach of mixed pricing. The LSG also considers such a legal regulation feasible and demands it, respectively. Both general reimbursement exclusions and a manipulable system of subgroup-based reimbursement amounts must be avoided to ensure and maintain high-quality medical care.

3. The physician information system must not control medical prescription

It should be added in this context that the physician information system (PIS) still contains certain limitations. To start off with, the industry supports the project „better physician information". However, this idea from the discussion platform called „Pharmadialog" must be properly implemented. The last sentence of the PIS section in the report on their findings states: „The therapeutic freedom of physicians is strengthened."[18] We need guidelines to promote the approach of providing better information to physicians via the practice software and stop lines to effectively prevent that the physician information system from evolving into a tool for physician control via sub-statutory provisions as a consequence of unclear specifications by regulators.



Quelle: Eigene Darstellung

Abbildung 3: Der Mischpreis stellt die wirtschaftliche Versorgung aller Patientengruppen sicher.

G-BA decisions should not be confused with therapeutic advices for physicians. The G-BA does not evaluate and decide about the therapeutic significance of evaluated pharmaceuticals in the actual medical care situation. It only evaluates the additional benefit of a certain pharmaceutical against a comparative treatment. The G-BA's decision „additional benefit proven" should thus not be interpreted as an individual treatment recommendation to refrain from prescribing a certain pharmaceutical.

High-quality therapy decisions in the treatment of patients are generally based on three fundamental pillars. These include a) best available external evidence, b) the physician's clinical expertise in consideration of the patient-individual treatment situation, as well as c) patient preferences. If these conditions are met, treatment decisions comply with the principle of evidence-based medicine which is also based on these three pillars.

Guidelines of several medical-scientific professional associations provide the best available external evidence for physicians. They are based on current scientific findings outlining relevant treatment algorithms. They provide updated treatment recommendations considering changes of the current state of scientific findings. Guidelines evaluate new pharmaceuticals not least in comparison with all others available alternatives in the indication in order to determine the therapeutic significance for the healthcare landscape. Thus, guidelines consider the total available evidence in the therapeutic area and more practice-related aspects of clinical practice.

In principle, external evidence can be a useful addition to the clinical expertise of the attending physician, but cannot replace it. Only medical experience and therapeutic freedom can cope with the individual treatment situation. A decision has to be taken as to how these findings or recommendations from external evidence are applicable for certain patients ensuring the optimal treatment decision for every patient. For this reason, guidelines should be understood as corridors of action and decision which may be deviated from in justified cases. In the individual situation, this can be done in accordance with the principle of indication, consultation, and participative decision-making. A patient-oriented preference determination is of special importance.

Sackett's pioneering statement (1997) should also be kept in mind which is regarded as the leading publication on evidence-based medicine[19]: „Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient." In all this, it should also be considered that the G-BA – as mentioned above – does not even consider half of the studies and thus the best available external evidence. Thus, a controlling physician information system would jeopardise evidence-based medicine (Figure 4).

The following example illustrates that20: For the indication of non-small cell lung cancer (NSCLC), the G-BA decision and guideline recommendations vary in eight of nine pharmaceuticals or 17 of 27 patient groups, respectively. For all of them, no – or where applicable only a partial – additional benefit was granted. In the guideline, however, the respective patient group was normally recommended as a viable treatment alternative.

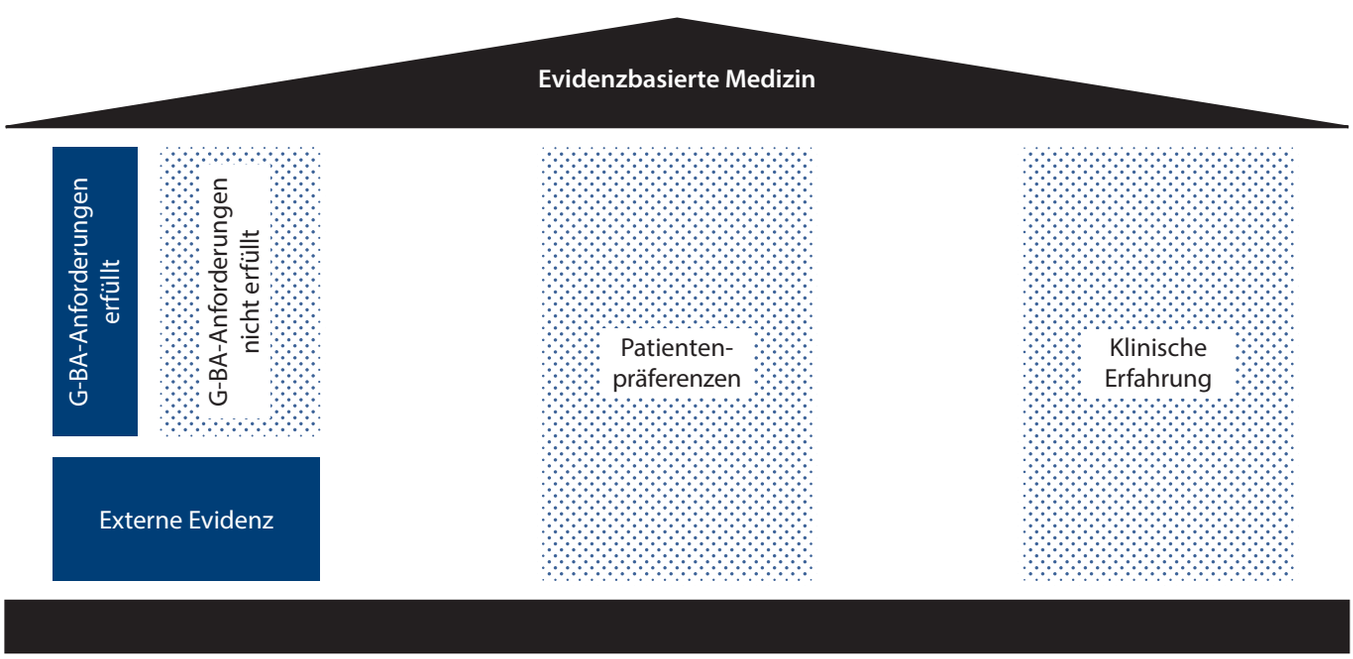
In Figure 5, pharmaceuticals which such a partial contradiction are highlighted in yellow and those with a complete contradiction are highlighted in red. For example, the guideline recommends the anti-cancer drug crizotinib as therapy without alternative for patients with ROS1-positive advanced non-small cell lung cancer. From a treatment perspective, this contradiction between G-BA decision and guideline recommendation is of particular significance, as

there is no adequate treatment alternative for these patients. Thus, the guideline on NSCLC shows in how many cases and under which circumstances high-quality medical care relies on pharmaceuticals, even if the G-BA has not proven an additional benefit for them.

The example was taken from a current investigation including systematic comparison of the clinical guidelines of the DGHO with G-BA decisions on the example of oncology and evaluation of two aspects: Coherence or contradiction regarding patient grouping as well as coherence or contradiction of G-BA additional benefit decision and guideline recommendations. It can be concluded that G-BA decisions are not suitable for prescription control: In 38 percent of the cases, G-BA decision and guideline demonstrate partial or complete deviations in terms of patient groups. In 60 percent of all patient groups, a partial or complete contradiction was observed across all tumour types between the G-BA decision and guideline regarding the additional benefit.

The results of the study show – on the example of oncology – that G-BA decisions neither correspond to the actual treatment situation with regard to patient grouping nor in terms of additional benefit assessment. They are thus neither suitable for treatment recommendation nor prescripti-

Drei Säulen der evidenzbasierten Medizin



Quelle: Eigene Darstellung

Abbildung 4: Ein steuerndes Arztinformationssystem gefährdet die evidenzbasierte Medizin.

on control. Prescription control on the basis of the G-BA decision would thus result in a substantial deterioration of medical care, as pharmaceuticals without proven additional benefit are also feasible and required for many patients according to the treatment guideline. The authors of the guideline are not alone with their opinion as the common statement by the National Association of Statutory Health Insurance Physicians (KBV), Association of Statutory Health Insurance Physicians Westphalia-Lippe, German Medical Association, Medicines Commission of German Physicians, German Hospital Federation, Association of the Scientific Medical Societies in Germany (AWMF), and BAG Patient Group (BAG Selbsthilfe) shows[21].

If – like health insurances propagate it – prescription recommendations will in fact be generated for the physician and integrated into the practice software, the project Physician Information System gets a whole new dimension[22]. It's not by chance that a certain pharmaceutical is automatically classified as a consequence of G-BA decisions, but the contents of G-BA decisions and guidelines for the respective indication must be continuously synchronised. Implementation proposals by health insurances largely ignore this substantive problem reducing it to a mere technical challenge. AMNOG decisions only needed to be linked „technically" and „interpretatively" to be able to integrate valid treatment recommendations into the software. It is suggested that the G-BA simultaneously determines these links within the scope of the AMNOG process. This will not work, and that is not the point at issue – for the real goals of health insurances are control and prescription control.

Moreover, it should be emphasised: A „traffic light system" is only a specific form of graphical representation. Physicians can be controlled without a traffic light system. According to the ideas of health insurances, G-BA decisions shall be displayed in the practice software on a context-sensitive basis during the prescription procedure. Visual highlights, such as colour codes or other visual signs shall facilitate orientation for the physician. Moreover, the results of the additional benefit assessment by the G-BA shall be linked to the information about the efficiency of a certain pharmaceutical. On this basis, the software indicates in which cases the physician should prescribe a certain pharmaceutical and in which cases its prescription might lead to a recourse. In such a scenario, health insurances would have direct control over the physicians' prescription behaviour.

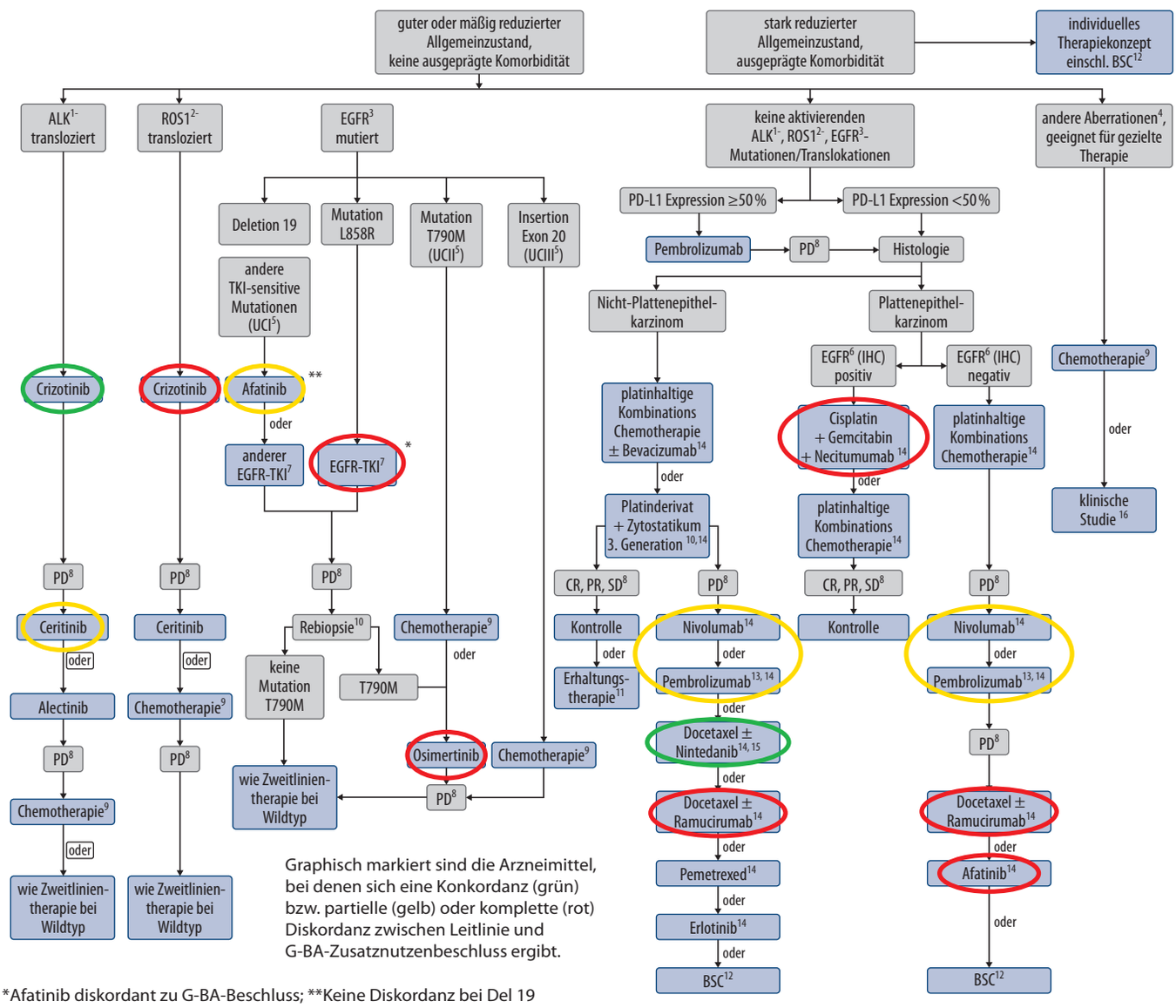
4. Conclusions

It was shown that the two alternatives of the mixed price – subgroup-based reimbursement or partial reimbursement exclusion, respectively – are inferior options. They are associated with significant disadvantages for the treatment of patients with innovative pharmaceuticals. Mixed prices are constitutive of AMNOG and feasible solutions to ensure high-quality medical care.

Moreover, it has been shown that an AMNOG system aimed at pricing cannot be a criterion for a physician information system. A physician information system that is used for prescription control will lead AMNOG down the wrong path.

Legislators and regulators are now asked to do the right thing: Establish the legal framework for mixed pricing and a physician information system aimed at providing information to the physician while preventing the risk of prescription control.

Onkopedia-Leitlinie zum NSCLC 2017 und Widersprüche zu G-BA-Beschlüssen



*Afatinib diskordant zu G-BA-Beschluss; **Keine Diskordanz bei Del 19

Quelle: Darstellung nach Holzerny, P, Werner, S, Rouf, J, 2018, Sind G-BA Beschlüsse für die Versorgungssteuerung geeignet? in: Gesundheitsökonomie und Qualitätsmanagement, im Internet unter http: dx.doi.org/10.1055/s-0043-121590, Zugriff am 28.05.2018, S. 7, auf Basis von Griesinger, F, Eberhardt, W et al., 2017, Lungenkarzinom, nichtkleinzellig (NSCLC): Leitlinie. Stand: 04.2017, im Internet unter: *https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-nicht-kleinzelligensclc/@@view/html/index.html* , Zugriff am: 15.05.2017

Abbildung 5: Das Beispiel NSCLC macht den Widerspruch von G-BA Beschluss und Leitlinienempfehlung deutlich.

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[4] See in this context also from a legal perspective Huster, S, 2017, „Mischpreis und Nutzenmonetarisierung" (Mixed price and benifit monetisation), in: Neue Zeitschrift für Sozialrecht, Series 26, Vol. 18, p. 681–686 as well as Huster, S, Harney, K, 2018, „Das Arztinformationssystem zwischen Information und Steuerung" (The Physician Information System in between information and control), in: Pharma Recht Volume 2/2018, p. 55-61. Cf. Sodan, H, Ferlemann, J, 2018, „Erstattungsbeträge für innovative Arzneimittel – Mischpreisbildung und gerichtliche Kontrolle" (Reimbursement amounts for innovative pharmaceuticals - mixed pricing and judicial control), in: Pharma Recht Volume 5/2018, p. 239-246.

[5] vfa AMNOG procedure database; last update 14 February 2018.

[6] Section 130b Paragraph 3 SGB V.

[7] vfa AMNOG procedure database; last update 14 February 2018.

[8] See details in Chapter 3.

[9] vfa AMNOG procedure database; last update 14 February 2018.

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[12] Internal assessment on the basis of 110 completed procedures for pharmaceuticals that underwent both the Fench and G-BA assessment (last update July 2015).

[13] See vfa, 2018, „Versorgungsprobleme in Deutschland durch Parallelhandel mit Medikamenten" (Problems of supply in Germany due to parallel trade with pharmaceuticals), on the internet at:
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[14] Also see Wey, C, 2017, „Zur Effizienz des Mischpreises" (On the efficiency of the mixed price), Brief expertise on the mixed price, on behalf of the vfa.

[15] Against this background, the intended restrictions by the LSG that only patient numbers from the G-BA decision shall be considered, is difficult in practice and contradicts the AMNOG negotiation principle. Thus, the pharmaceutical might be better in reality as the G-BA determination, or certain prevalences in the G-BA decision might not correspond to reality or experience another development than predicted. Moreover, the G-BA decision in combination with the regional efficiency audit have an influence on the development in reality.

[16] Cf. GKV-Spitzenverband, 2016, Opinion of the GKV-Spitzenverbandes of 9 December 2016 on the draft law on Strengthening Pharmaceutical Supply in Statutory Health Insurance (AMVSG), p. 44: „Mengenvereinbarungen sind bereits heute fester Bestandteil aller Verträge nach § 130b SGB V" (Volume agreements are already an integral part of all contracts according to Section 130b SBG V).

[17] From a legal perspective also see Huster, S, 2017, „Mischpreis und Nutzenmonetarisierung" (Mixed price and benifit monetisation), in: loc. cit., p. 681-686, as well as Sodan, H, Ferlemann, J, „Erstattungsbeträge für innovative Arzneimittel – Mischpreisbildung und gerichtliche Kontrolle" (Reimbursement amounts for innovative pharmaceuticals - mixed pricing and judicial control), loc. cit., p. 239-246.

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[22] For the legal limitations of the implementation of the Physician Information System see Huster, S, Harney, K: „Das Arztinformationssystem zwischen Information und Steuerung" (Physician Information System in between Information and Control), in: Pharma Recht Volume 2/2018, p. 55-61.

Implementation of the Physician Information System – an iterative, conflictual process

By Dr Florian Staeck

The decision of the Berlin-Brandenburg Superior State Social Court (LSG) on mixed pricing has caused ongoing uncertainty among prescribing physicians, statutory health insurances, and pharmaceutical companies.

Although the determination of reimbursement amounts on the basis of mixed prices has become common practice since the introduction of Statutory Health Insurance (German Pharmaceutical Market Reorganisation Act, AMNOG), the court's judgement left room for different interpretations regarding the application of the law. These interpretation options must be clarified by the Federal Social Court in a pending proceeding. Otherwise, the legislator should specify under which conditions prescription of a certain pharmaceutical – for which an additional benefit has been granted by the Federal Joint Committee (G-BA) – in a subgroup is considered economical. On an interim basis, efforts should be made to validate the underlying assumption empirically, i.e. whether the estimated prevalences of the G-BA decision is reflected in the actual prescription environment. Such an approach is considered appropriate by the majority of the participants of the 7th meeting of the Interdisciplinary Platform on Benefit Assessment in Kelkheim, Germany, on 9/10 March 2018. The main topic of the discussions was: „Prescription control after the AMNOG procedure: Physician Information System and mixed prices put to the test".

As during the 6th Platform Meeting in autumn 2017, opposing arguments put forward by the representatives of various interpretive approaches collided. On the one hand, it was concluded that a uniform reimbursement amount cannot be equally economical for all patient groups. In his obitor dictum, the LSG Berlin-Brandenburg stated that mixed prices in subgroups without additional benefit must not result in higher prices than for the ACT. Benefit-oriented reimbursement would be a logical consequence in the mid-term, since the legislator had accepted mixed pricing and creating of subgroups in numerous legal acts for years to account for the efficiency principle. This requires, however, subgroup encoding by physicians. Almost half of the subgroups is currently not encodable and thus not detectable in the prescription data of statutory health insurances.

The promise of a „carefree prescription"

Moreover, participants claimed that it was unclear whether the legislator could guarantee efficiency of the mixed price for an individual prescription. The argument that a „carefree" prescription could be safeguarded by means of specific provisions related to the status „exempt from efficiency audits" would be misleading. "Exempt from efficiency audits" would almost be an invitation for reviewers to take a closer look at individual cases. And physician would have to furnish proof in the individual case to fulfil the relevant requirements for a quality-secured prescription.

Representatives of the opposite position warned to generally call the mixed price instrument in question, as it has always created a fair balance by means of negotiation or arbitration in the past: Since the manufacturer would agree to an average price in the patient group for which an additional benefit has been granted by the G-BA and statutory health insurances would also agree to an average price in the group without proven additional benefit. Participants recalled that AMNOG's methodology was developed for price determination of new pharmaceuticals. The attempt to make this method perfect during operation to achieve an instrument for prescription control might lead us down the wrong path. Moreover, an additional encoding of subgroups in case of a benefit-oriented reimbursement would be extremely vulnerable to strategies in view

of the competition among statutory health insurances for assignments from the healthcare fund. And the level of bureaucracy for a large number of subgroups for which new codes would have to be created shouldn't be neglected.

Furthermore, it should be taken into consideration that challenging the mixed price would ultimately mean favouring partial prescription exclusions. As a consequence, patients could only be treated with the presumably equivalent appropriate comparative treatment (ACT). This would be questionable from a medical point of view, as the early benefit assessment would only be a snapshot of the available evidence. Since a non-proven additional benefit would not necessarily mean that the approved pharmaceutical had no therapeutic significance. It would be indispensable in those cases where standard comparative treatment was not effective or the patient did not tolerate it. Any prescription despite partial prescription exclusions would thus result in individual recourse claims by statutory health insurances. Participants emphasised that there was no legal basis for partial reimbursement exclusions in the early benefit assessment. In such a case, reimbursement exclusion needed to be specified in Annex 3 of the German Drug Prescription Directive (AM-RL).

Against this background, participants emphasised that legal clarity is needed quickly. If the mixed price was in fact illegal – according to the oral reasons for the judgement in the albiglutide case – this would generally apply for the SGB V. And specific control variants of the mixed price, e.g. within the scope of the framework agreement, would not rectify this illegality. The debate continued that it would then be the legislator's turn if the Federal Social Court would not address this fundamental question in the pending proceeding. Politics could have no interest in a situation of permanent legal uncertainty.

What does „additional benefit not proven" mean?

Participants noted that stakeholders still lack the will to classify the term „additional benefit not proven" more precisely. Controversially discussed partial reimbursement exclusion would thus only make sense in case of profound knowledge about the ACT and lack of data about the pharmaceutical to be used. Participants were also critical of the fact that additional benefits were still not updated on a regular basis. In a continuously rotating system it should be possible to update those benefit assessments regularly, where feasible. As the assessment of a new pharmaceutical could only be a snapshot at the time of the approval, many of them become outdated as they have not time limitation. This would for example apply for hepatitis C treatment where the regimen has undergone rapid and fundamental changes in the past years.

There was controversy on potential solutions for the issue raised by the Superior State Social Court that other proportions than those related to the mixed price would lead to benefit-related price distortions. Consequently, the focus should be on aligning the structure of mixed price quantities used for price determination as exactly as possible with actual prescription data. Usually, prescription shares of the G-BA decision would not provide a reliable basis, as they are only estimated prescription shares based on the dossier provided by the manufacturer. Epidemiologically well-validated data on morbidity would not be systematically collected in Germany. Moreover, the G-BA decision was based on the unrealistic assumption of full market penetration of the new product.

Participants made concrete suggestions for such an adjustment. Further clarification would be required as to what extent prevalence shares of each subgroup as defined by the G-BA were reflected in the claims data of statutory health insurances. Theoretically, in many cases it would

be quite possible to determine the severity of the disease via the ICD 10 code or concomitant or previous treatment via the ATC code, respectively. However, the subgroup could only be determined with sufficient precision in approximately 50 percent of the cases. Some participants summed up that the determination of precise prescription shares would not be possible without additional encoding by physicians. Moreover, statutory health insurances only had „Morbi-RSA" data that were usually two years old. Therefore, additional encoding by physicians would be required and should be specified and clarified by the legislator, e.g. in Section 84 SGB V.

Many participants support the following statement: If prescription of a „mixed price pharmaceutical" is appropriate in an individual case and prescription shares correspond to those used as a basis for the calculation of the mixed price, this prescription should generally be considered economical. If jurisdiction fails to clarify this issue, the legislator should make adjustments here, too.

Another proposed alternative was to have prescription shares in subgroups determined by means of a representative physician panel. In this case, collection of data of all physicians – which would be far more complex – would not be needed. Some participants welcomed this proposal and considered it „interesting", while others expressed doubts as to whether representative panels for prescriptions could be determined in all subgroups. Participants pointed out that the less common the disease, the more complete data collection would have to be.

Mixed price issue affects the PIS

Others advocated using the potential of almost 300 benefit assessments that have already been performed. It should be investigated, to what extent the prescription shares for the respective patient groups as estimated by the G-BA were reflected in actual prescriptions. Moreover, participants reminded of price-volume agreements that the legislator has requested. In their opinion, they are a comparatively easy and practicable alternative to protect statutory health insurances from marketing-motivated abuses by pharmaceutical companies.

The discussion showed that the legal and methodological ambiguities regarding the handling of mixed prices have a direct impact on the design of the PIS that has not yet been specified by regulators. The purpose of the PIS is to support physicians in their evidence-based medical therapy decision. A PIS that is based on AMNOG assessments allowing for prescription control would lead us down the wrong path.

During the discussion, various challenges emerged concerning the right „format" for the provision of information of physicians in the PIS. This demonstrates the variety and complexity of the provided information. If the user has selected a certain pharmaceutical and is looking for further details in the PIS, the following information shall be displayed, inter alia:

- reference to other pharmaceuticals with the same indication that underwent benefit assessment;
- current state of the information and validity period regarding time limitation;
- indication of the ACT selected by the pharmaceutical company as well as available study data regarding endpoints; and
- information on the annual treatment costs for the evaluated active substance and the ACT.

It was emphasised that in particular the justification of the G-BA decision needed to be „translated", since physicians would not read them otherwise. The complexity of the PIS would be further increased, if several „decision generati-

ons“ on individual active substances or combinations of active substances should be linked. This would be particularly important, if previous treatment options have changed in the meantime or the classification of risk patients were modified. One of the special challenges in the PIS was the representation of guidelines, as the certification catalogue for practice management systems (PVS) does not include this item. And if the PIS was integrated into it, the question arises which of them will be the „trump guideline“.

Participants, who are familiar with this legal topic, emphasised that including guidelines into the PIS was not, in principle, inconsistent with the law. However, this complex task could only be addressed as an iterative process. Other participants warned not to overstuff the PIS, as this would make the system susceptible to manipulation and compromise its acceptance among physicians. Against this background, the basic functions of the PIS should first be carefully examined.

Finally, participants of the 7th Platform Meeting were convinced that even if the Federal Ministry of Health issued a clarifying regulation on the specification of the PIS, its implementation and transcription into the physicians‘ PVS would probably be a conflictual process accompanied by extensive debate. Rapid and practicable solutions could thus not be expected.

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INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

Physician information via software: Orientation or control?

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