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Patients and medical societies: Additional expertise for AMNOG

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Goals of the plattform

Since the introduction of AMNOG in 2011, Germany has a well-established and widely accepted „adaptive system" for the assessment of the patient-relevant additional benefit (Health Technology Assessment, HTA). The assessment of the additional benefit by the Federal Joint Committee (G-BA) is the result of expert work based on a law (AMNOG) and procedural and methodical regulations.

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 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 qualified 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 as well as applied and further developed,
- Determining whether and to what extent 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,
- dentifying 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, e. g. on the further development of the legal framework conditions of AMNOG.

Moreover, the European perspective in HTA of innovative pharmaceuticals was reinforced by the European Commission's proposal for a Regulation on HTA in 2018. Monitoring the conflict between the well-established national assessment and the intended European HTA harmonisation is also a central concern of the platform. 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, an interdisciplinary 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 e.V.), and Xcenda GmbH.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Medical experience and the patient perspective – „head and heart“ for AMNOG

By Professor Jörg Ruof

Since 2011, the AMNOG procedure has been determining the handling of new launches or indication extensions of pharmaceuticals in Germany. Even though pricing between the pharmaceutical company and the National Association of Statutory Health Insurance Funds (GKV Spitzenverband) is at the end of every AMNOG procedure, the influence of these procedures extends far beyond pure pricing and influences both medical-clinical thinking and the availability of innovative pharmaceutical procedures for the treatment of patients.

In this context, patient organisations and the medical societies involved in the AMNOG procedure play an important role in accordance with the „triad of evidence-based medicine“, supplementing the frequently technocratic assessment of data sets with the patient's perspective as well as the physician's assessment and experience in order to balance „head and heart“ in the decision making.

Reason enough for the Interdisciplinary Platform for Benefit Assessment to address the „additional expertise“ that patient organisations and professional associations contribute during these procedures. In the past, the platform has established a successful way of bringing a wide range of speakers together. The first five articles address the patient perspective:

- As a nurse, communications scientist and state and federal politician for The Greens, Ms. Kordula Schulz-Asche emphasises the need to give the interests of patients a greater voice in self-governance – right up to voting rights in procedural matters or the election of an impartial member of the G-BA.
- Professor Dierks and Mr. Grimalauskas also call for hearing and co-decision rights for patient representatives and put forward concrete proposals on how the necessary legitimacy could be achieved by redesigning the system of pa-

tient representation.

- The two articles of patient representatives – Dr Danner as well as Mr. Geissler and Mr. Huber – impressively demonstrate what has already been achieved by patient representation both at national and European level, despite limited financial resources and infrastructure. Patient participation is a firmly established component of the German AMNOG assessment. The goal at European level is to be involved in research processes at eye level and early course setting of clinical development.
- The discussion on the topic of patient representation was very intensive and was continued even after the meeting. Thus – a novelty in this publication series – the wish of Dr Bausch, the „founding father" of this platform, arose to write an additional article on the topic in a kind of retrospective and prospective perspective: „Patient representatives in the G-BA: Is there really a need for reform". In consultation with the platform's advisory board, this request was granted – and I would like to expressly encourage you to „have a look" here.

On the second day, the vivid discussion continued on the participation of the medical societies:

- Professor Wörmann gave an interesting overview of the central role of the medical societies in the AMNOG procedure in his opening lecture on the topic of „Medical societies in the AMNOG procedure – a „non-quantifiable additional benefit"?", including the involvement in early consultation that has been introduced in 2020.
- Heterogeneous experience and perspectives of different medical societies and specialist fields are outlined in the subsequent articles of Professors Scherer & Braun (German Society for General Medicine), Professor Falkai with his employees Mrs. Streb and Dr Schüle (Neurology & Psychiatry) and Professor Seufferlein and Dr Bruns (German Cancer Society).
- General medicine plays a special role in comparison with the other medical societies due to its focus on the whole person and its integrative task. This leads to assessments and guideline recommendations that repeatedly differ from the recommendations of other medical societies.
- Despite the significance of mental illnesses and the high unmet medical need, there are hardly any innovative pharmaceutical treatment approaches. Moreover, it was often difficult to find a common definition of an appropriate comparative treatment.
- Oncology is very frequently represented in AMNOG procedures and is therefore very actively involved in all relating procedures. The improved participation in the definition of the appropriate comparative treatment should be highlighted. In contrast, there are still contradicting assessments in the AMNOG procedures, e.g. in the evaluation of endpoints.
- In his concluding presentation, Professor Ullmann emphasises the great importance of the participation of medical societies in the AMNOG procedure from the political perspective and refers particularly to the Act for Greater Safety in the Supply of Medicines (GSAV), which lays the foundation for greater participation of the scientific medical societies.

Please enjoy reading this publication. Our sincere thanks go to the sponsors of the conference – without them, this discussion would not be possible.

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The role of patients in the AMNOG procedure from the The Green's point of view

Kordula Schulz-Asche | Member of the German Bundestag

For more than a year now, the Corona pandemic, which has still not been overcome, has emphasised the importance of a secure and reliable supply of pharmaceuticals and vaccines. However, gaps that have become apparent in this crisis, such as supply bottlenecks or reliable access to pharmaceuticals at fair prices, have been known for a long time. Health policy is always a shift somewhere in-between the further development of good health and pharmaceutical care and the interests of numerous stakeholders. The tenth anniversary of the German Pharmaceutical Market Reorganisation Act (AMNOG) is a good opportunity to review how existing set screws function and make adjustments where necessary. At the time, the AMNOG was a breakthrough in terms of an increased benefit orientation and performance-based prices in the pharmaceutical market. Over time, however, it became apparent that the original political goal of the AMNOG was only achieved to a limited extent, namely to set prices of pharmaceutical on the basis of their added value and thus keep costs in the healthcare system within reasonable limits. Today, more sales are generated for fewer patented pharmaceuticals than ten years ago – a sign that ever higher prices are being called for individual pharmaceuticals. The challenges of the future, which will predominantly be reflected in affordable pharmacotherapy for patients, can only be addressed to a limited extent with the existing system. In the future, it will be even more important to establish suitable models for superior quality assurance in the pharmaceutical sector and fair prices, and to further develop AMNOG – which was conceived from the outset as a learning system – in benefit assessment and pricing. Always with the goal in mind to be guided by the needs of patients, provide good and reliable health care, and keep healthcare expenditures within reasonable limits. The past has shown how important experience and advice from clinical practice have been and continue to be in promoting reasonable adjustments to the AMNOG process. Health policy has long been the profession of experts, but it has always been regarded as very complex and complicated, since a wide variety of stakeholders and thus a wide variety of interests – that are often diametrically opposed – have to be taken into account. At the same time, health policy is something that affects us all - but for us Greens, „patient orientation" in the health sector has not yet gone far enough. There are numerous examples of this. Patients should have sovereignty over their health data and be given fair access to the therapies they need. Furthermore, a good supply of pharmaceuticals should not depend on the financial means of the respective state. Independent and comprehensible information and support, quality transparency and the strengthening of patients' rights vis-à-vis service providers and health insurers are essential elements of a health care system that respects their self-determination and transforms them from sufferers into stakeholders within the treatment process. But how can patient participation be ensured or advanced in a complex system such as pharmaceutical benefit assessment? Patient representatives suggest time and again to listen more to those affected as well as to self-help organisations and integrating practical experience into the opinion-forming process. This suggestion runs through the various areas of application and is reasonable from a green perspective. In order to better respect the interests of patients in self-administration, an enhanced personnel and financial support for patient representation is required. We Greens demand that patient representatives be given more rights, such as the voting right in procedural matters, election of an impartial member of the Federal Joint Committee (G-BA), or greater consideration in other institutions of self-administration. Theoretical knowledge from science, politics and

health economics plays a major role in the benefit assessment of pharmaceuticals. However, it is also important to include the patients' perspective in the process, as their participation is equally important. In order to be able to make a proper and comprehensive assessment, a patient bank is therefore needed that can meet the other banks at eye level. In view of the prioritisation of research and development in the pharmaceutical sector, patient-oriented needs should also be reflected in research projects, which is currently not the case. Research is mainly conducted on drugs for those indications generating the highest profits. As a result, infectious diseases and rare diseases, for example, are neglected. From a global perspective, this aspect is all the more important, because we are still seeing less research into therapies for diseases that occur primarily in the global south. In the future, patients will hopefully have an even louder voice when it comes to shaping their healthcare. As health policy actors, we should not oppose this, but enable and encourage participation. At best, we should not only think about the future of health policy at national level, but also at European and international level, in order to be prepared for future health crises.

Kordula Schulz-Asche, *nurse and communications scientist, member of the German Bundestag (Alliance 90/The Greens) since 2013, member of the Bundestag Committee on Health. In her parliamentary group, she is responsible for nursing care policy and policy on the elderly. She was state chairwoman of Alliance 90/The Greens in Hesse from 2005 to 2013. She was a member of the Hessian state parliament for ten years, where she was, among other things, the health policy spokesperson for her state parliamentary group. She lived in Africa for 13 years and worked, among other things, for the German Society for International Cooperation (Deutsche Gesellschaft für Internationale Zusammenarbeit, GIZ), the German Development Service (Deutscher Entwicklungsdienst, DED) in the field of health education and in the GIZ project „HIV/AIDS Control in Developing Countries".*

Options of patient participation – a view of the legal framework

Professor Christian Dierks, Antanas Grimalauskas | Dierks+Company Rechtsanwaltsgesellschaft mbH

Section 140f of the German Social Code, Book V, the Patient Participation Ordinance pursuant to Section 140g SCB V, and the Rules of Procedure of the Joint Federal Committee (G-BA) provide the legal framework for patient participation in the statutory health insurance. At present, patient representatives in the G-BA are nominated by the „relevant organisations" and have co-counselling rights in the decisions of the G-BA. However, patient representatives should also have consultation and co-decision rights. For this purpose, the patient representatives' decisions must be legitimised, which can be achieved by redesigning the system of patient representation. The increasing importance of health data will further strengthen the central role of patients in the development of the healthcare system.

Key parameters of patient involvement

Patient participation in the healthcare system as a creator and decision maker is an important and socially accepted goal. The 2013 Patient Rights Act was a major step towards improving patient participation in healthcare. Under this act, the right of application of the relevant patient interest representative organisations in the G-BA was strengthened[1].

In Germany, basic decisions regarding statutory health insurance are made by the legislature in the SGB V. However, at various points in the SGB V, it is the G-BA's responsibility to substantiate the entitlement of patients with statutory health insurance to benefits in accordance with the generally accepted current state of medical knowledge and specify appropriate quality assurance measures for practices and hospitals.

The decisions of the G-BA, which are usually made in form of directives, are indirectly input-legitimised by the legislator's decisions and their output monitored within the framework of the legal supervision of the Federal Ministry of Health (BMG). Consequently, the participation of patients in the healthcare system of the statutory health insurance system also requires participation in the decisions of the G-BA.

2. Structure of patient representation

Section 140f (2) SGB V provides the legal basis for the participation of patient representation „in matters relating to healthcare". It specifies that patient representatives should have a right of co-counselling, a right of attendance and a right of filing applications in the G-BA. However, participation in the G-BA is only possible for the „organisations that are decisive for the representation of the interests of patients and self-help for chronically ill and disabled people at federal level".

These relevant organisations are determined within the framework of the regulation of the Federal Ministry of Health (Patient Participation Ordinance). According to paragraph 2, section 1 of the PatBeteiligungsV, the German Council for the Disabled (Deutscher Behindertenrat), the Federal Working Group of Patients' Agencies (Bundesarbeitsgemeinschaft der PatientInnenstellen), the German Working Group of Self-Help Groups (Deutsche Arbeitsgemeinschaft Selbsthilfegruppen e. V.), and the Federation of German Consumer Organisations (Verbraucherzentrale Bundesverband e. V.) are considered relevant organisations. Thus, the question arises as to whether this one-time determination of relevance should be regularly reviewed and analysed. If organisations other than the „relevant" ones are denied participation with reference to the fact that they are not relevant, because they were not determined to be relevant, this could be an obstacle for the representation of the actual patient interests.

According to Section 140f (2) Sentence 3 SGB V, the number of patient representatives in a committee may not exceed the number of members delegated to this committee by the German National Association of Statutory Health Insurance Funds (GKV-Spitzenverband). For this reason, relevant organisations may delegate up to five members to the plenum of the G-BA and up to six members to the subcommittee Pharmaceuticals. Since the majority of patient representatives at the G-BA come from the member associations of the BAG SELBSTHILFE, the latter coordinates the delegation of patient representatives to the G-BA on behalf of the persons specified in the Patient Participation Ordinance[2].

3. Rights of the representatives

Section 140f SCB V, the Patient Participation Ordinance, and the G-BA's Rules of Procedure and Rules of Procedure provide the basis for the rights of patient representatives in the G-BA. In addition to the aforementioned co-counselling, attendance and application rights, these patient representatives have speaking rights, information rights and claims to reimbursement of travel expenses, compensation for loss of earnings and a lump sum for their time expenditure (Section 140f (5) SGB V). The representatives thus have

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a fairly well-developed right of co-determination. However, they don't have consultation and co-decision rights in the G-BA. The representatives of the relevant organisations participate in the consultations without any voting right and have no right to justification of diverging decisions.

Jurisprudential literature has long called to strengthen the rights of patient representatives[3]. In particular, voting rights and a veto on certain issues by patient representatives have been raised as important means to improve patient participation in healthcare issues. It should be noted, however, these means of design tools are problematic without input legitimation of the patient representatives' decisions. Therefore, alternative models of patient participation should be explored.

4. Options for improving patient representation

A voting right for patient representatives is not feasible without legitimising their participation. This could be achieved by ensuring that patient representatives are not appointed by the relevant organisations, but elected by the German Bundestag, e.g. for a period of five years. At present, the power of selection lies with the relevant organisations that have been pre-selected by law which results in a lack of legitimation of the representatives neglecting the representation of patient groups that are not included.

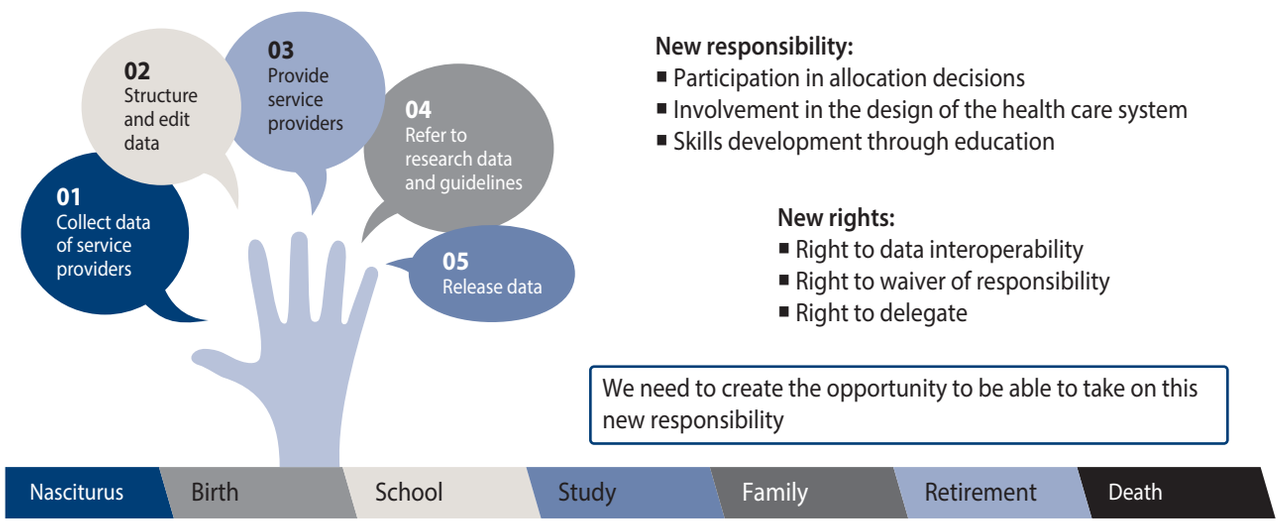
Participation of a broader range of patients in healthcare can only be ensured, if all citizens are given the opportunity that their interests are represented in the G-BA. Therefore, all citizens should be able to apply for accreditation as patient representative in the G-BA after their suitability has been assessed and confirmed by the BMG. Qualification criteria could be described in the Patient Participation Ordinance and should include, in particular, patient competence, professional and system expertise. The elected patient representatives should attend training courses to maintain their suitability. The time spent by the patient representatives should be appropriately reimbursed in accordance with Section 140f (5) SGB V.

Cooperation between the elected representatives should also be improved to increase transparency and thus make their work more comprehensible for all patients. In addition, patient representatives should not be required to vote unanimously. Such an obligation reduces the effectiveness of patient representatives and jeopardise their individual legitimation.

5. Digitisation strengthens patient centredness

Regardless of the legal design of patient representation, digitisation will secure the central role of patients in the further development of healthcare. Data are the most important basis of modern medicine, and patients will have the dispositional power over the majority of data. Over the course of a person's life, health insurers, physicians, caregivers, and nurses will change. But patients remain as a continuum in terms of the personal data pool[4]. The increasing role of health data will tremendously change the position of patients within the healthcare system. Patients will no longer be the „affected parties" hoping for legislative decisions to strengthen their participation rights. Digitisation will strengthen the patient-centredness of healthcare so that patients play a key role in healthcare decisions. However, new rights will associated with new responsibilities: In future, patients will need to participate in allocation decisions, engage in the design of the healthcare system, and develop their own competence through education. Therefore, further opportunities must be created to support patients in assuming this responsibility with educational programmes similar to those in Section 20k SCB V, in order to achieve the continuous improvement of healthcare with patient competence and preference decisions.

Digitisation strengthens patient centredness



Source: Dierks & Company

Figure 1: The increasing role of health data will drastically change the position of patients in the healthcare system - digitalisation will strengthen patient-centredness.

References

[1] Gesetzesentwurf der Bundesregierung, BT-Drs. 17/10488. https://go.sn.pub/L52tF6

[2] BAG Selbsthilfe: Patientenbeteiligung, abrufbar unter: https://go.sn.pub/9ZjbwJ

[3] Francke, R. / Hart, D.: Bürgerbeteiligung, 214; Klafki, A. / Loer, K.: Verwaltungsarchiv 108 (3), 343-365; Kingreen, T.: VSSAR 2019, 155-172; Pitschas, R.: MedR 2006, 451-457; Sodan, H. / Hadank, B.: NZS 2018, 804-809; Huster, S.: RPG 2015, 10-13; Gassner, U.: NZS 2016, 121-127.

[4] Dierks, C.: Bundesgesundheitsbl 2019 (62) 1113-1119. https://go.sn.pub/239Yof

Patients in the early benefit assessment – a field report

Dr Martin Danner | BAG Selbsthilfe

Since the concept of benefit is based on so-called patient-relevant endpoints, patient participation is not an optional accessory in the HTA process of benefit assessment in Germany, but one of the methodological principles of the assessment procedure. Due to the well-established structures of patient and self-help organisations in Germany, this mandatory participation can be implemented consistently. The basis for this specific involvement is the qualification and empowerment of patient representatives by the respective bodies. This empowerment in turn forms the basis for a stronger patient orientation of care, independent of specific assessment procedures.

The goal of benefit assessment in the German healthcare system is to only add those diagnostic and therapeutic options to the statutory health insurances' catalogue of services that have an additional benefit as compared to the existing care options. The benefit assessment of new pharmaceuticals under the AMNOG is just a use case of this basic principle. Section 35a of the German Social Code, Book Five (SGB V) also specifies another basic idea: The benefit concept shall be aligned with so-called patient-relevant endpoints.

This procedure will also set the course for patient participation: The consideration of the patient perspective in the HTA process is not an optional accessory or an experiment in democratic theory, but part of the methodology to determine the actual patient relevance, which must be central focus of the evidence of benefit to be provided. This should always be kept in mind, even when comparisons are made with participation processes in other countries or when theoretical participation models are derived from overarching maxims:

If, in other healthcare systems, it is more a matter of dealing with questions of rationing healthcare services ethically or via forms of participation that promote acceptance, patient participation gets the connotation of citizen participation. If the discussion is about compensating for legitimacy deficits of HTA bodies reaching theoretical questions about democracy, this raises the question of whether a plus in legitimacy can be achieved through patient participation.

None of these aspects play a central role in patient participation within the scope of the AMNOG process. This is about integrating patient competence to clarify patient relevance of endpoints, but also about providing a certain control function in the methodological evaluation of study

designs and outcomes. By making sure that the patient side also appreciates them, biased interpretations of certain data by other stakeholders can be prevented more easily.

This multifunctional approach is also taken into account by the organisations that have been appointed to delegate patient representatives in accordance with Section 140f SGB V. Fortunately, in Germany we can rely on a widespread network of patient counselling institutions, self-help groups and self-help organisations, and social associations. Even before the introduction of patient participation in the healthcare sector, we already had cross-indication associations of patients for almost every disease pattern. Since these groups are organised as associations, democratic decision-making structures ensure that statements on healthcare needs, concerns and demands can be addressed to the bodies not only by individuals, but also by patient groups. Application experiences on diagnostic and therapeutic options are also discussed and aggregated in patient organisations. This is why organisations under Section 140f SGB V have been able to delegate people with specific patient competence to healthcare expert committees for almost 20 years now.

However, patient competence alone is not sufficient to be able to exist in the committees. Patient representatives must also be able to deal with the sometimes highly complex regulatory requirements for HTA procedures and complex methodological requirements for study evaluations. Moreover, they must have the necessary rhetorical skills to represent their own positions in committees that are often characterised by long-standing traditions.

It is an outstanding achievement of patient organisations in Germany – also in international comparison – that they have successfully build up a network of volunteer experts who have this specialist knowledge. Together with the full-time staff of the patient organisations, these individuals provide the professional background of patient representation. The different competence profiles in the patient organisations can be used specifically for the participation of patient representation in the benefit assessment procedures. So-called topic-related representatives as well as so-called permanent representatives with general competence are delegated to the respective committees of the Federal Joint Committee (G-BA) contributing patient-relevant information to the evaluation process. This comprises knowledge of the partially quite complicated regulations of the AMNOG process, knowledge of the decision-making maxims of the stakeholders authorised to make decisions, and above all methodical knowledge for the evaluation of study designs and outcomes.

Dr Martin Danner *is a lawyer and the national managing director of the Federal Association of Self-Help for People with Disabilities and Chronic Illnesses and their Relatives (BAG SELBSTHILFE). After his studies in Heidelberg, he worked as a lawyer for several years specialising in health law before taking over as head of the health policy and self-help promotion department of BAG SELBSTHILFE. He is the spokesman for patient representation at the G-BA and, among other things, participates in the Scientific Advisory Board of the Medical Centre for Quality in Medicine (AZQ) and in the IQWiG Board of Trustees.*

It is certainly a very positive development that some people who have participated several times or intensively in assessment procedures as a topic-related representative can later make use of this general competence. This has quite positive effects on the understanding of evidence-based medicine in the counselling work of self-help and beyond the mere benefit assessment of pharmaceuticals. However, the number of people gradually increases who do not only provide their expertise but also their legal knowledge, methodological expertise and rhetorical skills to healthcare bodies.

One could therefore say that structured and sustainable patient participation is also a process of patient empowerment. On the other hand, there is a certain degree of personnel fluctuation in patient representation. Therefore, it is important to constantly recruit new topic-related representatives to participate in the technical AMNOG process and introduce them to participation. Here it is very helpful, if permanent representatives take newcomers by the hand, while respectfully taking their input into consideration as valuable votes of patient representation. Often it is simply a matter of encouraging them to raise their voice in a committee of 40 to 50 renowned experts.

Employees of the Patient Involvement Specialist Team, who support the patient representatives, are located at the G-BA and play an equally important support role. According to Section 140f SGB V, the employees of the specialist team have the exclusive task of supporting patient representatives in their participation in the G-BA bodies. They thus have a different task than all other office employees. While they provide professional support for the decision-making processes of the G-BA while maintaining strict neutrality, the specialist team exclusively supports patient representatives (cf. Section 140f (6) SGB V). This support ranges from briefing new topic-related representatives on the procedures of the G-BA and conception and implementation of training events, to the organisation of voting meetings, formulation of applications, methodological review of study designs and outcomes, as well as submission of pre-coordinated votes of the patient representation.

This qualification process of representatives from patient organisations would not have been possible without the competent empowerment by the Patient Involvement Specialist Team. However, no matter how well-qualified the participants may be, they cannot become properly involved in benefit assessment procedures, if the conditions for participation there do not allow this.

It has also proven to be extremely important that patient representatives have not only been granted the right to submit comments, but a genuine right of co-counselling during the early benefit assessment. Often, data on the actual medical care situation, relevance of certain subpopulations, use of comparative treatments, or assessment of study data can only be provided in concrete terms with regard to the statements of the other stakeholders. Thus, a consensus vote of all participants is often achieved. The large percentage of consensual votes in the AMNOG procedures is an impressive example of this. The rather academic discussion on the voting rights of patient representatives is thus superfluous with regard to the AMNOG processes.

However, the AMNOG process sometimes causes patient representatives severe stomach pain: It is difficult to understand from the patient's point of view, if the provision of a certain dosage form or additional treatment option, for example in the treatment of seizure disorders, is classified as „irrelevant", since these circumstances cannot per se justify an additional benefit according to the regulations of the AMNOG process. And in these cases, it is not very helpful to point out that the core of the AMNOG process is

a pricing procedure, so that the additional benefit will primarily be reflected in the question of a higher price.

Especially instruments, such as the so-called physician information system for AMNOG pharmaceuticals show that it is of course also a matter of defining the range of therapeutic options. The more this screw is turned, the more the question arises as to whether the additional benefit should be determined more strongly by the routine use of the pharmaceuticals. Patient representatives also like to get involved in such methodological discourses. The rise of the endpoint of „improvement in quality of life" within the scope of benefit dimensions is a good example of this. It is true that from the outset, patient representatives have repeatedly emphasised that an improvement in quality of life can be a significant aspect in the determination of the added benefit of pharmaceuticals. However, it was not until the subsequent discussion of methods that the view that these were all merely subjective constructs could be gradually eliminated, so that a fairly stable standard has now been established with regard to the instruments and procedures for measuring the patient's individual quality of life.

Meanwhile, it is part of the well-established consideration process of the benefit assessment that the plausibility of assessment results on endpoints of morbidity or the prevention of side effects are always compared with data on the improvement of the quality of life. Similarly, outcomes on the extension of life are always evaluated, especially by patient representatives, against the background of how the patients' quality of life is affected by the time gained. At least from the patient representatives' point of view, especially in this sector patient participation has also led to a more patient-oriented design of the methods used in benefit assessment.

In summary, it can therefore be stated that the AMNOG benefit assessment does not only include patient participation, but virtually presupposes it. The goal of any benefit assessment in medicine must be to capture the needs of patients in the best possible way.

Health competence & participation in Germany and EU

Jan Geissler | Patvocates, EUPATI Germany, LeukaNET, Member of the Strategy Circle of the National Decade against Cancer, EU Cancer Mission Assembly, Ethics Committee of the Bavarian Medical Association, German CML Alliance, ISPOR Patient Roundtable Europe; Stefan Huber | Editor and Project Manager

In Germany, patient participation in research is still in its infancy, although patients can make a valuable contribution with their specific knowledge and experience already at the beginning of a research project. One of the goals of the National Decade against Cancer (Nationale Dekade gegen Krebs) is therefore to involve patients in the research process at eye level and to tailor health research to their individual needs. Essential prerequisites for this involvement are informed patients and educational courses, such as those offered by the European Patient Academy. At EU level, however, patient participation has been well established and strengthened by various EU initiatives.

The change from passive study participants to partners at eye level in pharmaceutical research is a development that has been increasingly promoted by patients in recent years, e.g. by participating in self-help groups, patient organisations as well as advisory bodies or ethics committees, and from which research can also benefit in the design and implementation of substantive and efficient studies: On the one hand, patients and their relatives have the best insight into life with a disease and its influence on the ability to work, social life or mental well-being, as well as their own view of the comprehensibility and appropriateness of patient information and specific experiential knowledge. On the other hand, they often have a different risk-benefit assessment than attending physicians, e.g. with regard to diagnostics, risks, side effects or quality of life, and can provide precise information about it.

A survey of patients, relatives, physicians and nurses by the European patient organization Myeloma Euronet in 2009[1] revealed that there is still a lot of unused potential in involving patients and their perspectives in health-related research. For myeloma patients, for example, hair loss, neuropathy or respiratory problems were considered to be treatment side effects with a major negative impact on their overall well-being, but the attending physicians considered them to be less problematic. On the other hand, physicians rated thrombotic events or jaw damage as significantly more serious than patients themselves.

In addition, research must be differentiated on the basis of the often very different needs of patients, because their preferences vary widely – even within subgroups of a disease. The problem here is that these needs are usually summarised under the so-called „patient voice“ and the heterogeneity of patients and their individual needs are neither adequately researched nor addressed. This was al-

so shown in a survey conducted by Myeloma UK[2] revealing that severe toxicity was rated higher among younger, working, and caring family members and those who had experienced severe toxicity more often (see figure 1).

Therefore, the goal of the National Decade Against Cancer, an initiative launched by the German Federal Ministry of Education and Research (BMBF) in spring of 2019, is to involve patients more – and at eye level – not only in care, but also in health research. In a statement, they emphasise: „Health research is only successful if it reaches people. We will therefore involve the society in oncology research topics, for example through self-help or other patient organisations. Citizens will thus be actively involved in the Decade and contribute additional perspectives and expertise."

Besides the Federal Ministry of Health, the BMBF was able to win partners from research, care and self-help as well as patient organisations for the initiative. A strategy group is the driving force that provides a framework for the initiative's activities with seven fields of action. It consists of members of the partner organisations of the Decade, with Jan Geißler being one of two patient representatives.

Three further work groups of the initiative address central research tasks and develop solution strategies: Generate knowledge by networking research and care with a focus on networking and systematic evaluation of research and care data, major unresolved issues in cancer research, about the strengths and weaknesses of German researchers, existing research gaps and potentials, comparison with international measures, and prevention with a focus

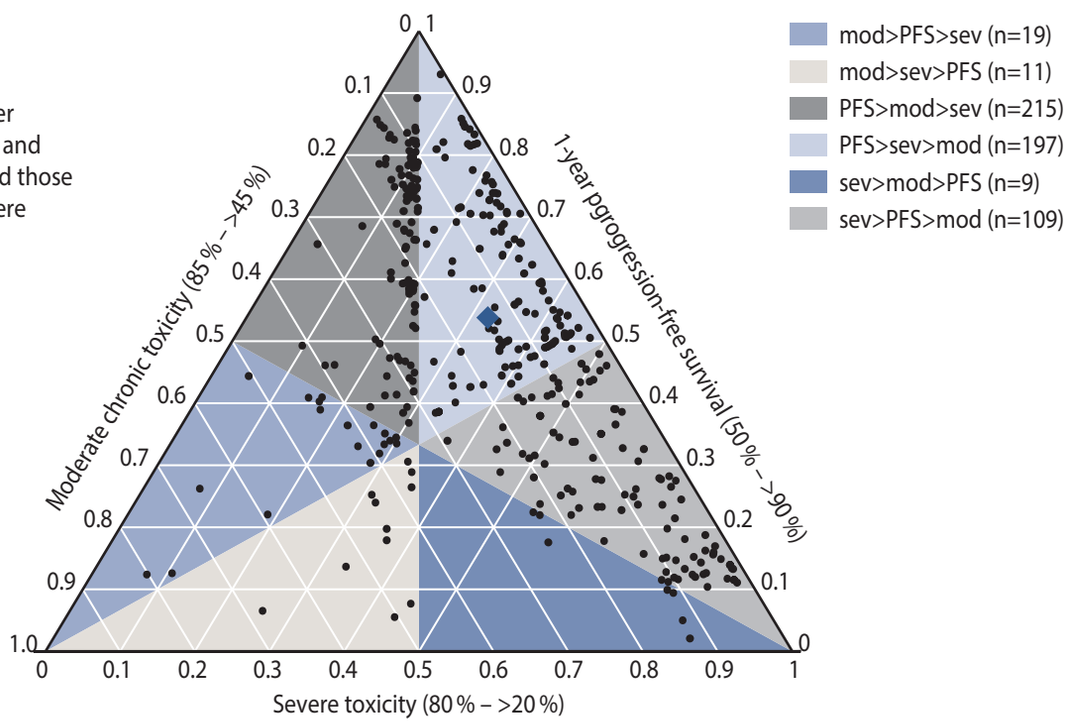
Since he was diagnosed with chronic myeloid leukaemia in 2001, **Jan Geißler** *has founded or co-founded, respectively, various patient organisations such as LeukaNET e. V. Moreover, he was director of the European Patient Academy EUPATI and still runs their German platform. He represents the patient perspective in committees and initiatives, such as the EU Cancer Mission Assembly or the National Decade against Cancer. He is also managing director of Patvocates, a think tank and consultancy for patient advocacy, health policy and medical research.*

After completing his studies in high school teaching and literature, **Stefan Huber** *worked as an editor at a publishing house where he was jointly responsible for various journals. Since autumn 2020, he has been engaged in editorial work and as a project manager for various patient organisations, including LeukaNET e. V.*

Participation in early stages has the greatest impact on results

In this example:

- Strong heterogeneity
- Severe toxicity rated higher among younger, working, and caring family members and those who had experienced severe toxicity more frequently



PFS = Progression free survival

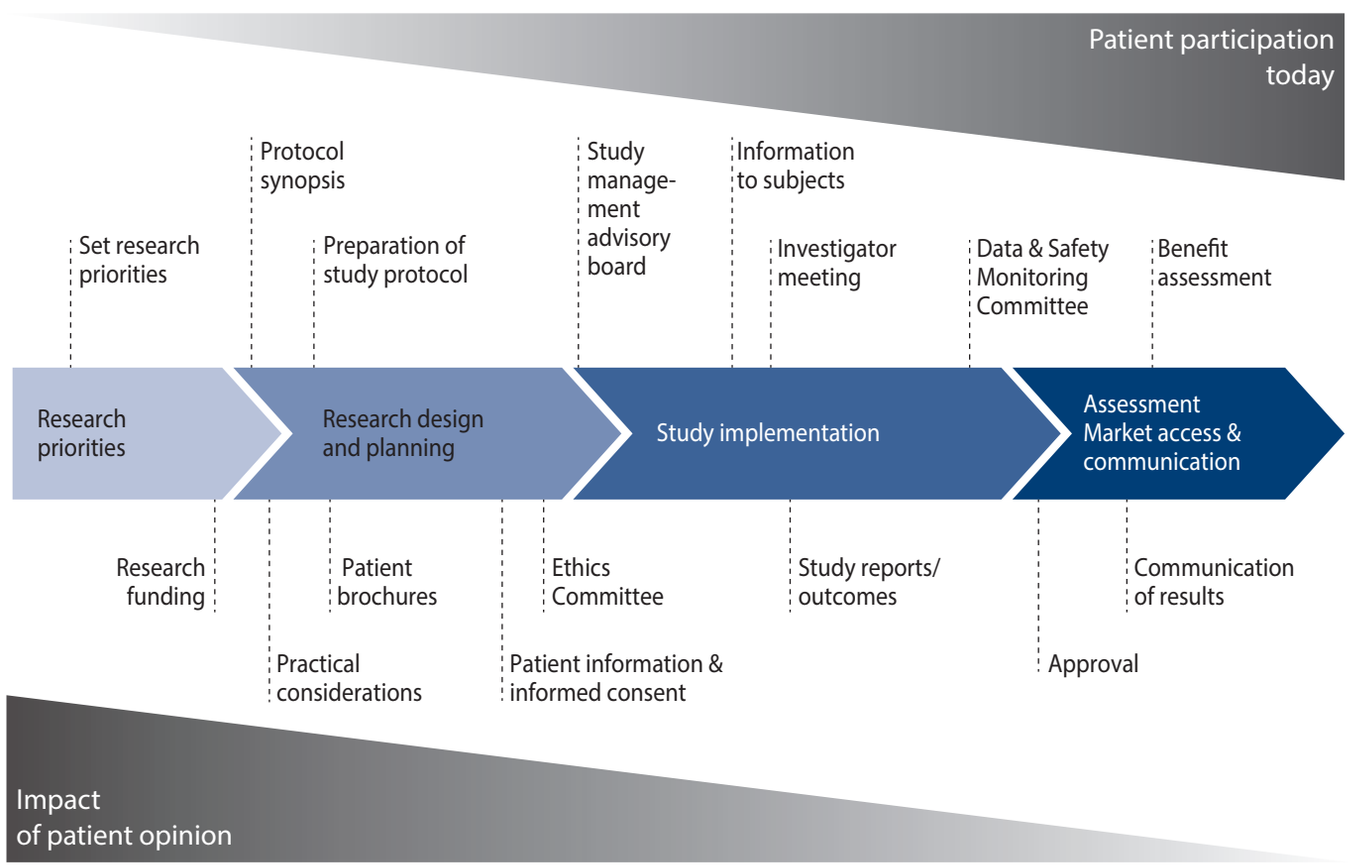
Source: Survey with 560 myeloma patients from the Myeloma UK, replicating the pilot of MPE, MPNE and EMA, D. Postmus et al. (2017) The Oncologist

Figure 1: Patients' preferences also vary within the subgroup of a disease. The heterogeneity of patients and their needs has not yet been sufficiently explored.

on cancer screening.

All of the activities of the Decade are based on the guiding principle of consistently aligning health research with the needs of patients at eye level. Accordingly, one of the seven fields of action focuses on strengthening patient participation in order to take greater account of the specific experiences and expertise of those affected in cancer research. In healthcare, for example, patients are already increasingly involved in the decision-making process - because their expectations regarding the quality of life and side effects often differ significantly from those of the attending physicians.

Participation in early stages has the greatest impact on results



Source: own presentation

Figure 2: The later patients are involved in the development process, the more difficult and less effective they can influence research priorities based on their needs.

However, German patients are still rarely involved in cancer research itself, for example in the design of clinical studies or research funding programs or in ethics committees. At present, patients are only involved towards the end of the research process, e.g. in questions of reimbursement or the communication of results, which is why an active participation and influence can often only take place in the evaluation of research decisions and results that have already been made. The later patients are involved in the development process, the more difficult and less effective they can

influence research priorities based on their needs. Yet it is because of their detailed insights into the everyday lives of people affected by the disease and related treatments, as well as their knowledge of expectations for future therapies, that it is helpful for all sides to involve patient representatives in the early stages of cancer research in order to redirect studies towards specific patient needs (see figure 2).

Therefore, the goal of the National Decade is to build a bridge between patients and cancer research, which is why a first survey was conducted in November 2019. The results showed that there is obviously some kind of communication barrier between patients and researchers: for example, with regard to questionnaires on quality of life that are difficult to understand as well as the desire for better research knowledge in patient organisations. Moreover, personnel, financial and time issues were mentioned, among others also that of an appropriate remuneration of patient representatives for their very time-consuming participation.

Participation depending on experience and competences

In order to enable patients to contribute their experience and knowledge as well-informed experts for patient concerns in the collaboration with researchers, authorities and ethics committees at eye level, appropriate training is required, such as that offered by the non-profit European Patient Academy EUPATI which is active in 18 countries. Besides guidelines for cooperation with patients in pharmaceutical research and in regulatory processes, EUPATI has developed the EUPATI Toolbox[3], an online knowledge research database that is easy to understand for laypersons. Moreover, the Patient Academy offers further education material and training in nine different languages as face-to-face events and webinars, e.g. on the basic principles of pharmaceutical research, but also on rhetoric and interview management or the use of social media. So far, the pan-European project, which is funded by the Innovative Medicines Initiative, has educated around 240 patient experts from various countries. Their online portal is used by some five million users.

Moreover, the Patient Academy was involved in a pilot project of the Paul Ehrlich Institute (PEI) and the Federal Institute for Drugs and Medical Devices (BfArM) on the participation of patient experts in approval procedures of the European Medicines Agency and has proposed potential patient experts in several procedures.

EUPATI's further education includes:

1. Basic research, pharmaceutical development planning
2. Pre-clinical development
3. Clinical research and studies
4. Regulatory and approval processes
5. Pharmaceutical safety, risk/benefit
6. Health economics and benefit assessment (HTA).

EUPATI's guidelines[4] stipulate where patient participation in the design of clinical studies can be applied; the intensity with which patients can participate depends on their individual skills. However, the term „patient" is often used imprecisely and does not sufficiently reflect the different types of potential contributions. Thus, depending on the level of information and representation, as well as the degree and nature of their skills, a distinction can be made between

- individual patients and caregivers: have a personal experience of living with a disease;
- patient advocates: have insight and experience with a larger patient population;
- patient organisation representatives: represent the views of a patient organisation;

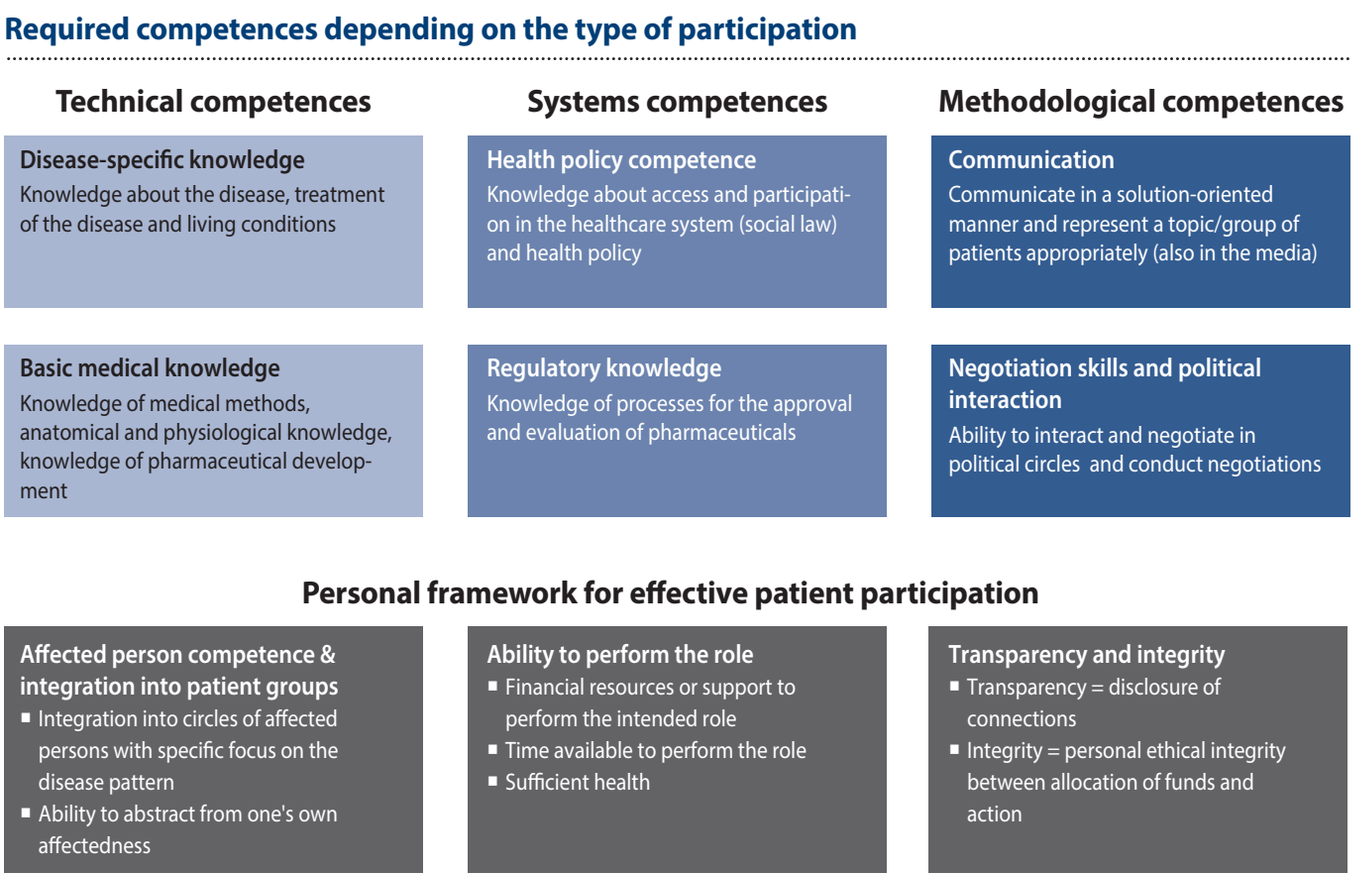


Figure 3: Depending on their level of knowledge, skills and expertise about their disease, patients can actively engage in therapy development at different points.

- patient experts: have additional technical knowledge in research and development and/or regulatory work.

Thus, depending on their level of knowledge, skills and expertise about their disease (see figure 3), patients may be actively involved in the development of treatment options at various points. For example, the can take an advisory role, provide advice as experts on a particular disease, or participate as equal partners in defining research needs. During the initial definition of research priorities, for example in the form of patient-relevant endpoints, and in research design and planning in the preparation of study protocols, inclusion and exclusion criteria and patient priorities in relation to benefit and risk – or the choice of measurement instruments for quality of life (QoL) and patient-reported

outcomes. These include data that supplement the evaluation of a therapeutic intervention with the patient's subjective assessment of, for example, on QoL, fatigue, or pain. They are increasingly being taken into account in medical research as they provide an additional patient perspective on the disease or treatment.

Currently, the EMA and US Food and Drug Administration (FDA) discuss with various stakeholders to find ways to standardise patient-generated data and the methods of data collection. In addition, the Innovative Medicines Initiative has initiated the SISAQOL project under the supervision of the European Organisation for Research and Treatment of Cancer (EORTC) to develop recommendations for the analysis and interpretation of PROs in clinical cancer studies.

But patients with low to medium expertise can also become involved in these early stages, for example in research funding or designing patient information and consent forms in patient-friendly language. If they are part of an ethics committee, patient representatives can also contribute to the critical dialogue about ethical issues in study design, inclusion and exclusion criteria, frequency of invasive diagnostics, risk-benefit balance for subjects, or data protection.

Patient participation is standard at EU level

At EU level, pharmaceutical approval, data protection and requirements for clinical studies are largely determined by EU legislation. Interestingly, patient participation in regulation and research has long been standard practice outside Germany. For example, patient representatives have been and continue to be involved in Horizon 2020, an EU research and innovation funding program, the Innovative Medicines Initiative (IMI), the Innovative Medicines Initiative 2 (IMI2), and in future also in the Innovative Health Initiative (IHI), which is expected to start this autumn, as external experts on advisory boards, review panels and – as sometimes required in calls for proposals – in research projects.

In addition, they are active partners in medical societies, e.g. as full members in the European Cancer Organisation, European Reference Networks, European Society for Medical Oncology (ESMO) and its Patient Advocacy Workgroup, EHA European Affairs Committee and EHA Patient Advocacy Workgroup. And for more than 15 years, they have also been represented in the EMA Board and all its committees – often with voting rights – as well as the Patients' and Consumers' Working Party (PCWP).

In addition, the new EU Regulation 536/2014 on clinical studies, which will come into force in January 2022, has introduced some significant changes from the patient perspective: for example, an increase in the public transparency of clinical studies and related data as well as study results, and the necessity to provide information in the protocol as to whether and how patients were involved in the preparation of the protocol. Similarly, the new regulation includes a requirement for patient participation in national ethics committees, which have been given the „power to issue opinions for the purposes of this Regulation, taking into account the views of lay people, in particular patients or patient organisations"[5].

Patient representatives have also contributed to the highly topical and complex issue of data protection, which is of particular relevance in the areas of clinical studies and healthcare at EU level, e.g. in a Patient Advisory Board, as participants in focus groups, and in a Delphi project on data protection and sharing in the multidisciplinary EU-funded project RD Connect (2012-2018), which brought together partners from the EU and beyond to create an integrated global infrastructure for rare disease research.

In Germany, self-help has been well established and participation in G-BA processes is well organised, but – despite their specific expertise, which is essential for research design and regulatory frameworks – patients are often excluded from systematic participation in research and research-related capacity building.

The National Decade against Cancer now offers a great opportunity for change here. Both at European and international level, patients have had a lot of influence on research design and funding programs for some time – but here, too, initiatives such as the EU Cancer Plan, the EU Cancer Mission, and the EU Trio Council Presidency shall further establish and consolidate patient participation, as the Trio Council Presidency of Germany, Portugal, and Slovenia emphasised in a joint paper: „Germany and the Trio Council partners will initiate a process to systematically involve patients in European cancer research [...] emphasising the importance of active patient involvement throughout the translational process from research to patient care. [...] The Trio Council Presidency will advance patient-centred cancer research as a standard in Europe."[6]

References

[1] Detecting Myeloma, ways to shortening an often painful and tedious patient odyssey: results from an international survey. Myeloma Euronet (2009). 314 physicians & nurses, 260 patients & carers, 43 countries. https://go.sn.pub/bxdM6m

[2] Survey with 560 myeloma patients from the Myeloma UK, replicating the pilot of MPE, MPNE and EMA, D. Postmus et al. (2017) The Oncologist. https://go.sn.pub/k8OBM7

[3] https://go.sn.pub/KVczLd

[4] Warner Kay, See Wolf, Haerry David, Klingmann Ingrid, Hunter Amy, May Matthew. 2018. EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D. Frontiers in Medicine. Volume 5. Figure 1. https://go.sn.pub/6ynB2s

[5] Verordnung (EU) Nr. 536/2014 des Europäischen Parlaments und des Rates vom 16. April 2014. https://go.sn.pub/5F3Zmb

[6] Trio Presidency of the Council of the European Union – Germany, Portugal and Slovenia Declaration on effective cancer research „Europe: Unite against Cancer". https://go.sn.pub/8PwVRn

Medical societies in the AMNOG procedure – a „non-quantifiable benefit“?

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

Availability and use of new pharmaceuticals in Germany are determined by three regulatory processes: Approval by the European Medicines Agency (EMA), early benefit assessment according to the AMNOG procedure by the Federal Joint Committee (G-BA), and guidelines of scientific medical societies. The specifications and recommendations of these procedures are consistent in many points, but can also differ substantially. This complicates decisions about the use of a new pharmaceutical in a specific treatment situation. Medical societies are involved in all three processes and represent an important connecting element. An early involvement of medical societies in the consultation of pharmaceutical companies by the G-BA, which has been implemented in 2020, is a further step towards the integration of medical science into the benefit assessment of pharmaceuticals and thus in the quality-assured care of patients.

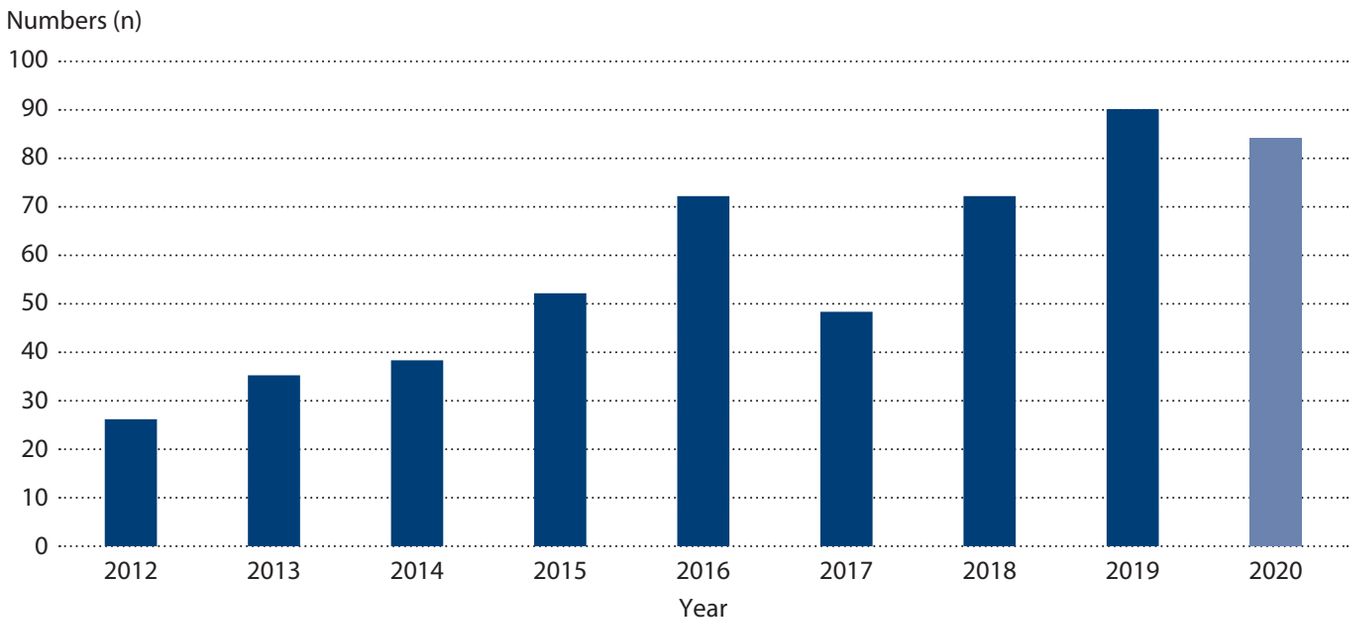
The flood of new pharmaceuticals, e.g. in oncology, is a blessing but can sometimes also be a curse. It is a blessing when new pharmaceuticals improve the prognosis of a disease, alleviate suffering and/or have fewer side effects than previous therapies. The term „new“ is also associated with hope, which many patients experience as a value in itself. We perceive the flood of new pharmaceuticals as a curse when they are marketed at great expense but do not present measurable improvements in patient-relevant outcomes, but also when the assessment of new pharmaceuticals by regulatory authorities, payers and physicians differs and a lot of valuable energy has to be invested for the individual access of patients.

In Germany, the Pharmaceutical Market Reorganisation Act (AMNOG) came into force on 1 January 2011 for the early benefit assessment of new pharmaceuticals as the basis for pricing[1]. The aim was to establish a system for a well-regulated access to new pharmaceuticals in due consideration of economic resources. The law of 2010 does not mention medical societies, but stipulates that an oral hearing is conducted. In the G-BA's Rules of Procedure, medical societies are among those entitled to submit comments.

In subsequent years, the „learning“ AMNOG system was adapted in several legislative procedures. In 2017, these included the comprehensive information for prescribing physicians in the Strengthening Pharmaceutical Supply in Statutory Health Insurance (GKV-AMVSG)[2] and in 2019, the Act for Greater Safety in the Supply of Medicines (GSAV), the early involvement of medical societies in the consultation of pharmaceutical companies by the G-BA[3].

In fact, these opinions are both a responsibility and a challenge for the medical societies.

Early benefit assessment procedures completed with a determination 2011 to 2020



Source: AWMF and DGHO: Early benefit assessment of new pharmaceuticals in Germany 2011-2020, pricing and more. May 2021, in print.

Figure 1: The number of assessment procedures has increased continuously since 2011. Reasons for this are not only new pharmaceuticals and/or new indications, but also re-evaluations of active substances with orphan drug status.

Professor Bernhard Wörmann *works as a physician specialising in internal medicine, haematology, and internal oncology and has an additional qualification in palliative care. Since 2010, he has been Medical Director of the German Society for Haematology and Medical Oncology (DGHO), and since 2015, he has been Chairman of the Commission Benefit Assessment of Drugs of the AWMF. Moreover, he works at the Outpatient Health Centre on the Virchow Campus of the Charité hospital in Berlin focusing on haematology, oncology and tumour immunology.*

Participation of medical societies in the early benefit assessment

The number of assessment procedures has increased continuously since 2011 (see figure 1[4]). This increase is mainly due to new pharmaceuticals and/or new indications. Other reasons include re-assessments after expiry of time limits and re-assessment of pharmaceuticals with orphan drug status that have exceeded the statutory sales volume of 50 million Euros. The approval of new pharmaceuticals varies greatly in the individual specialties (see figure 2[4]). The total number of procedures is higher than the total number of products evaluated. This is due to the fact that many pharmaceuticals are assigned to more than one specialty, e.g. oncology and pneumology in case of pharmaceuticals for the treatment of lung cancer, to diabetology and endocrinology in case of diabetes pharmaceuticals, or to haemostaseology, cardiology, and neurology in case of anticoagulants for the prophylaxis or therapy of vascular events.

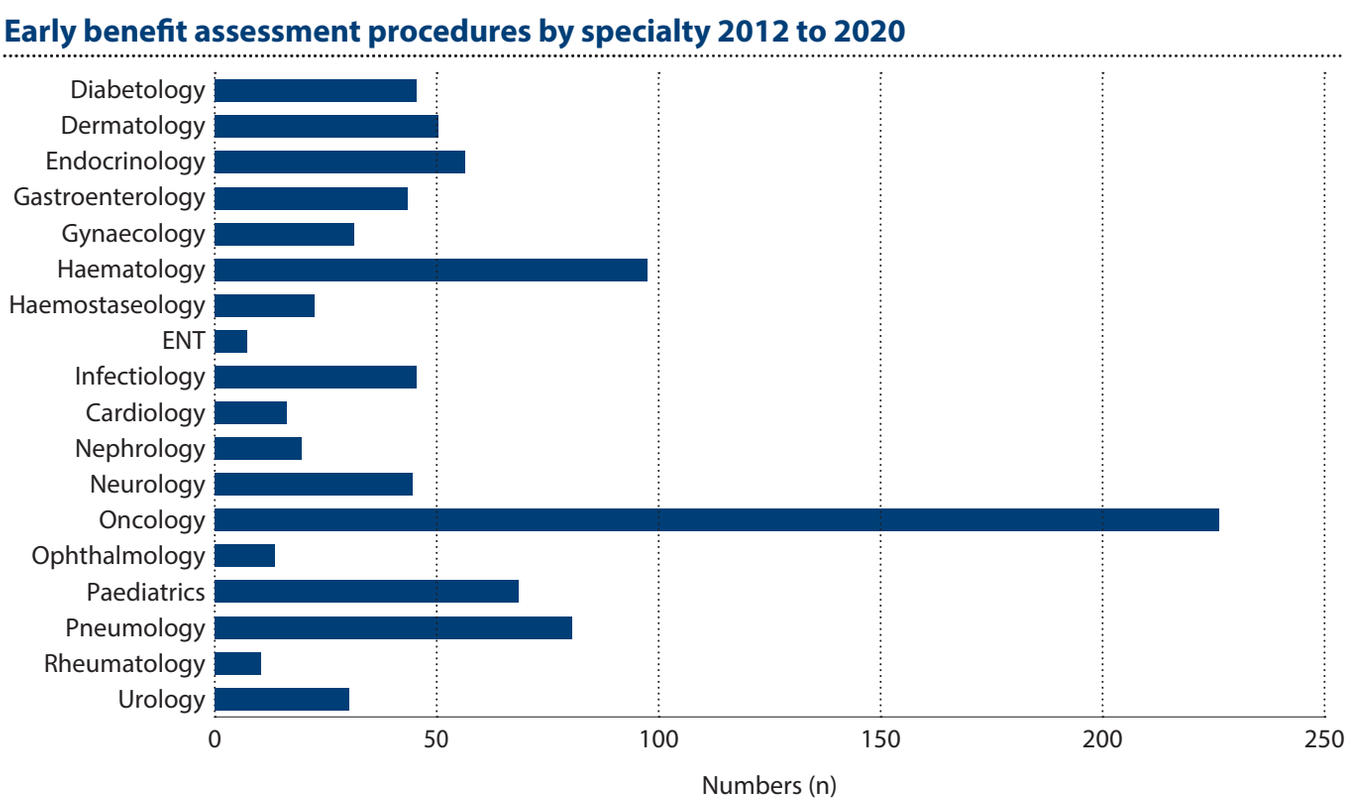


Figure 2: Approval of new pharmaceuticals varies widely across specialties. Often, drugs are assigned to more than one specialty, such as diabetology and endocrinology.

After publication of the reports of IQWiG or G-BA, medical societies are involved in the procedure as parties entitled to submit comments. Figure 3[4] shows the rate of participation over the past decade.

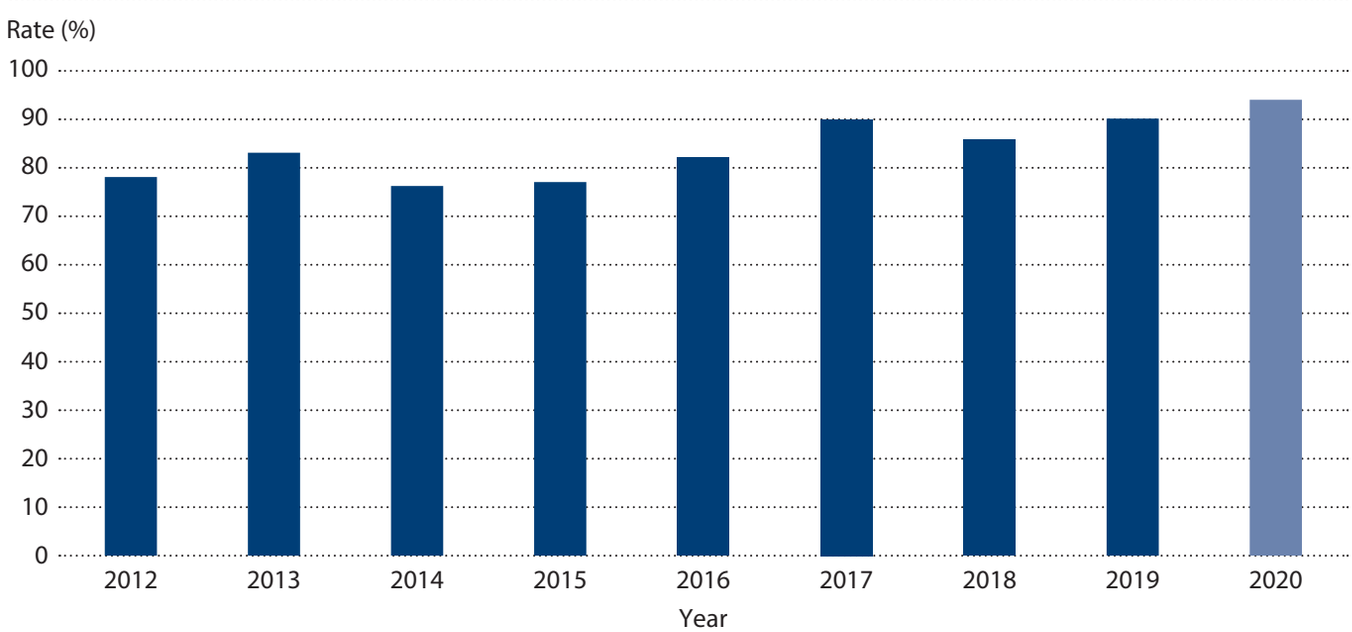
In 2020, medical societies participated in 94% of the early benefit assessment procedures. Thus, the increasing trend in participation continues at this high level. Several medical societies participated in numerous procedures (see figure 4[4]).

In the majority of the procedures, one single medical society is involved. If several medical societies are involved in a procedure, this mainly due to interdisciplinary indications, or indications for children/adolescents and adults, where both the paediatric and the adult medical society submit comments.

Influence of medical societies on the procedure

The direct influence of the medical societies on the procedure cannot be measured. An earlier, rough evaluation commissioned by a pharmaceutical company revealed that the G-BA agreed with the proposals of the medical societies in 51% of the procedures[5]. However, this did not sufficiently take into account the fact that many medical societies do not provide a dedicated assessment of either

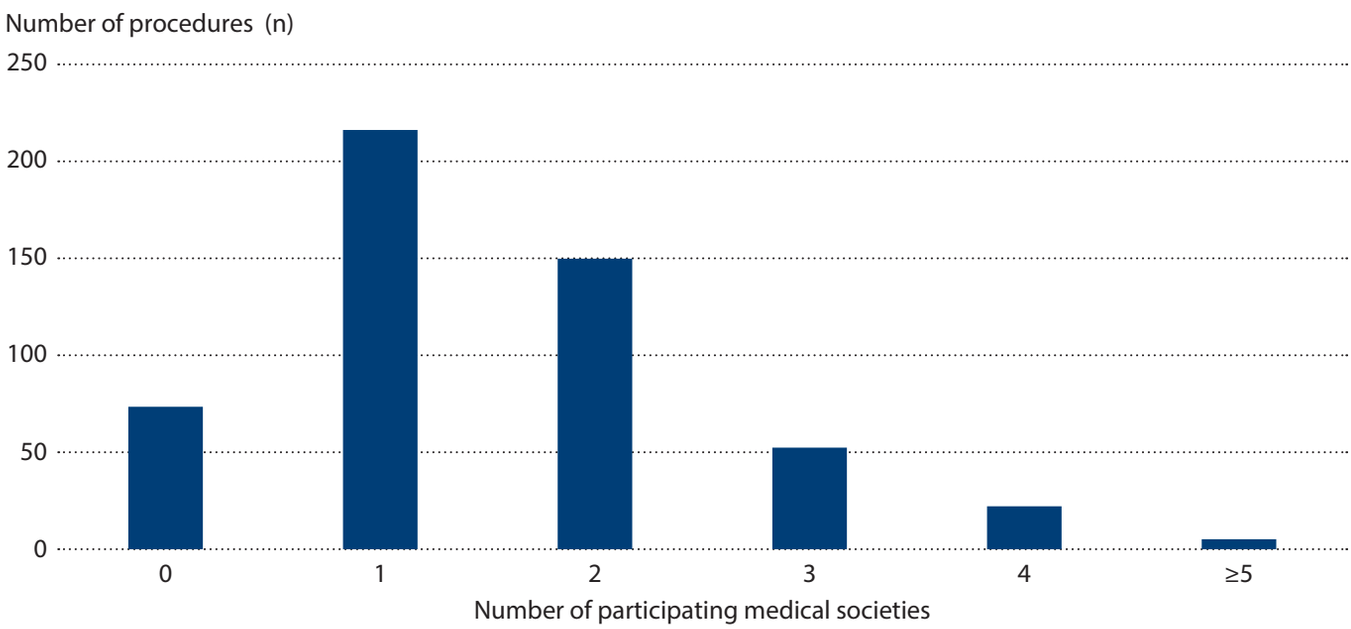
Rate of participation of medical societies in early benefit assessment procedures



Source: AWMF and DGHO: Early benefit assessment of new pharmaceuticals in Germany 2011-2020, pricing and more. May 2021, in print.

Figure 3: In 2020, medical societies were involved in 94% of all early benefit assessment procedures. Since 2010, the trend shows an increasing rate of participation.

Number of medical associations involved in the early benefit assessment



Source: AWMF and DGHO: Early benefit assessment of new pharmaceuticals in Germany 2011-2020, pricing and more. May 2021, in print.

Figure 4: More than one scientific medical society has been involved in numerous early benefit assessment procedures from 2011 to 2020.

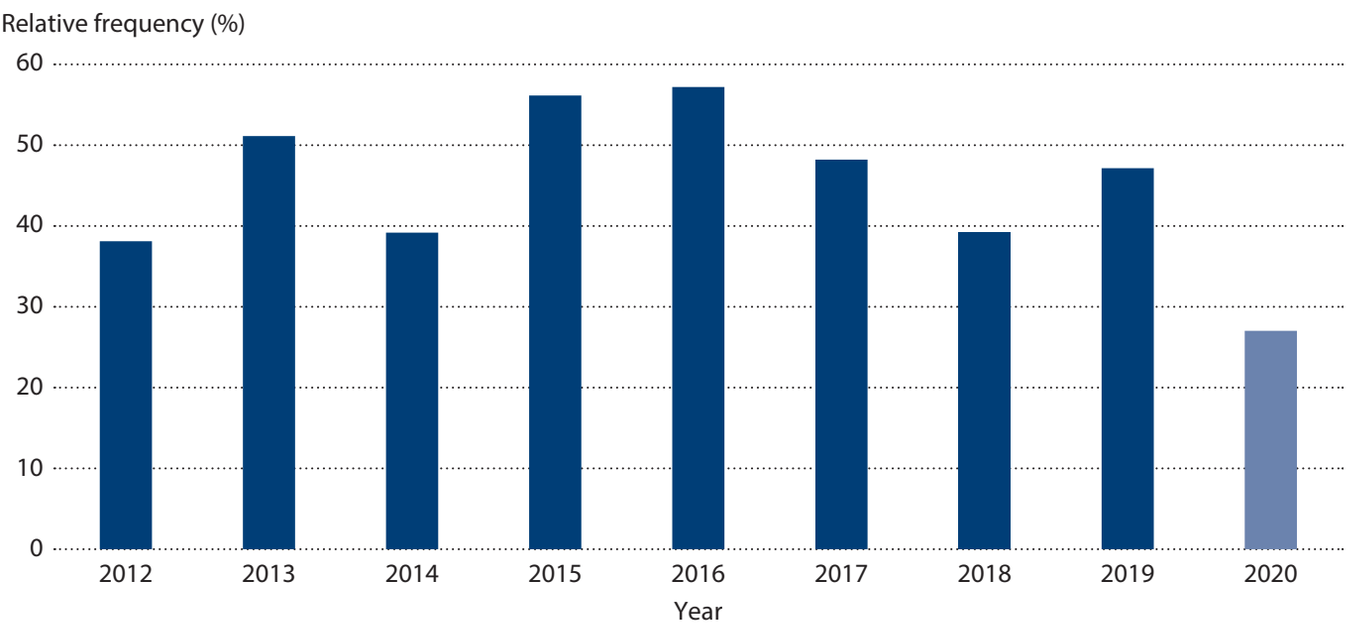
the overall procedure or the individual subpopulations, but understand their task more comprehensively:

- Evaluation of the dossier
  - Methodology, consultation
- Classification in therapy standard
  - Guidelines, care
- Experience
  - Efficacy, side effects.

Medical societies focus on content-related topics. A major challenge in the AMNOG process is the formation of subgroups/subpopulations as stipulated in the law[1]. Parameters include gender, age, disease severity or stage, centre and national effects. Here, the benefit assessment process differs significantly from the approval process. We use the terms „subgroups" and „subpopulations" together because both are used in the early benefit assessment process. Figure 5[4] shows the number of procedures where subgroups/subpopulations have been defined.

Medical societies had intensively dealt with the topic in 2015/2016[6]; it was also the subject of a complaint by a pharmaceutical company[7]. The number of procedures in which subgroups/subpopulations were defined as the basis for the appropriate comparative treatment and the assessments had increased to 57% in 2016. Since then, the

Frequency of subgroups/subpopulations in the early benefit assessment



Source: AWMF and DGHO: Early benefit assessment of new pharmaceuticals in Germany 2011-2020, pricing and more. May 2021, in print.

Figure 5: The number of procedures in which subgroups/subpopulations were defined as the basis for the appropriate comparative treatment reached its peaked in 2016 at 57% and has recently declined to 27%.

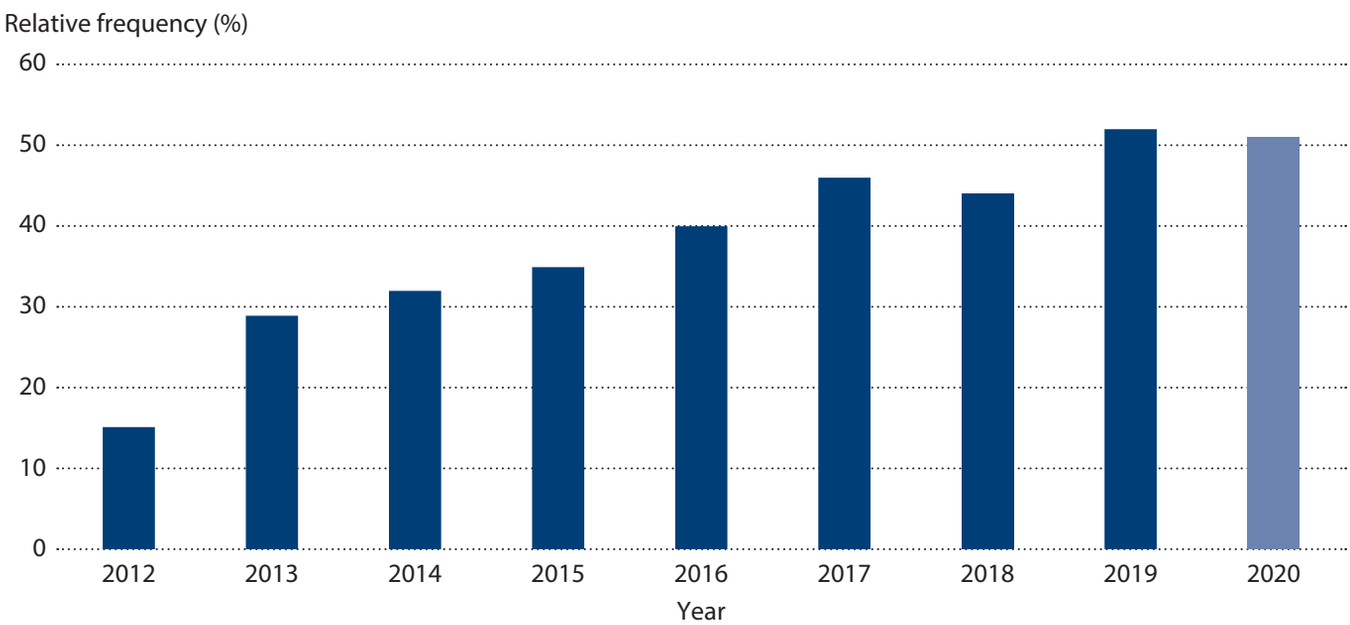
rate has steadily declined, reaching a low of 27% for all procedures that had been completed in 2020.

In the meantime, opinions of medical societies, discussion within the framework of the hearing and other factors frequently result in subsequent requests to the IQWiG to prepare an addendum or to the responsible department of the G-BA to prepare an amendment, respectively. Figure 6[4] shows the proportion of addenda/amendments in the total number of procedures. The number of procedures with addenda/amendments had further increased in 2019, and is now >50%. A frequent reason for these addenda/amendments on the part of the medical societies is criticism of the determination of the appropriate comparative treatment.

Discrepancies between AMNOG, approval and guidelines

All discrepancies between AMNOG and approval are best illustrated in the evaluation of the G-BA's determinations. By the end of 2020, 519 AMNOG procedures had been completed. Taking into account the definition of subgroups/subpopulations, the G-BA took 966 decisions. The results of all determinations from 2011 to 2020 are shown in figure 7[4]. Of all new drugs approved by the EMA and as-

Frequency of addenda/amendments in the early benefit assessment



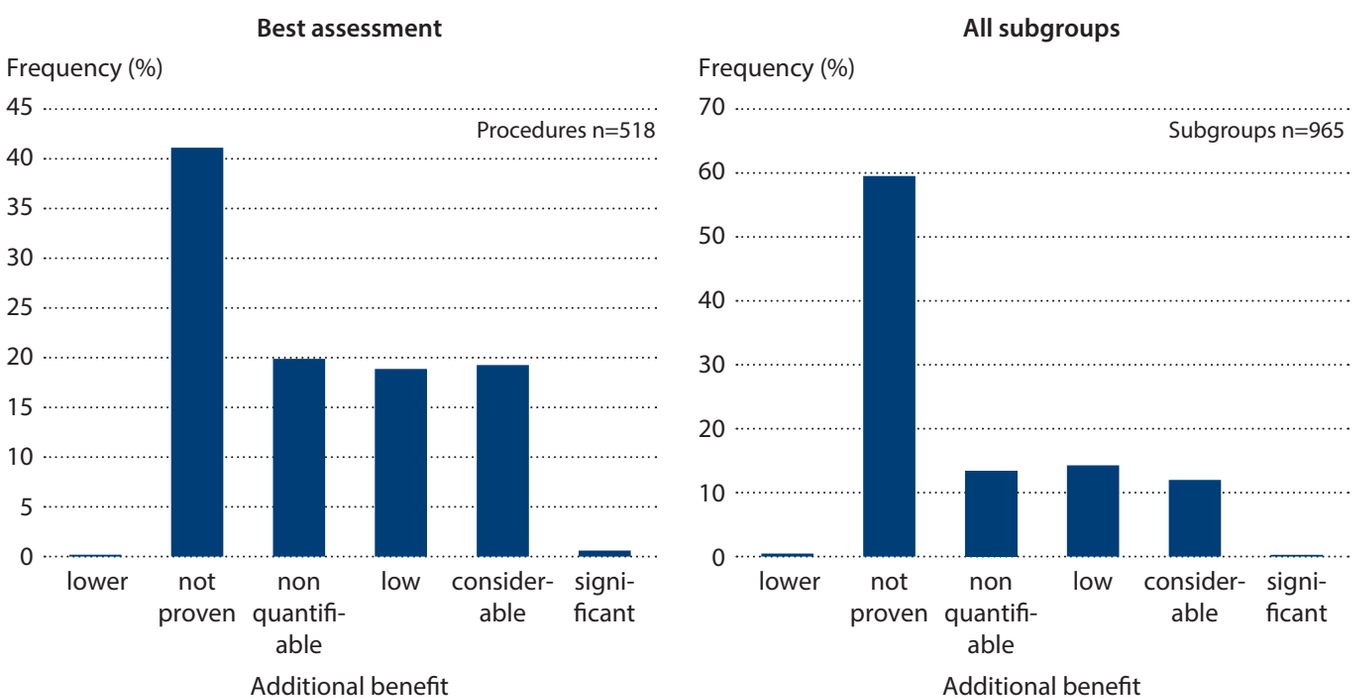
Source: AWMF and DGHO: Early benefit assessment of new pharmaceuticals in Germany 2011-2020, pricing and more. May 2021, in print.

Figure 6: Comments from medical societies and hearings increasingly lead to additional requests to the IQWiG to prepare an addendum or the G-BA to prepare an amendment.

sessed as effective and safe, the G-BA determined „additional benefit not proven" in 41.1% of all procedures. In 19.9% of the procedures, „not quantifiable" was the best rating, followed by 19.3% with „considerable" and 18.9% with „low" added benefit. In 0.5% of the procedures, the category „significant" was selected as the best rating, and in 0.2%, the overall harm was rated higher than the benefit. The evaluation by subgroups/subpopulations revealed that the added benefit was determined to be „not proven" in 59.6% of all procedures.

Discrepancies between early benefit assessments and guidelines are more difficult to detect. For oncology, we compared assessments according to the AMNOG process and the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO MCBS). ESMO MCBS differs substantially from the G-BA approach, primarily in that endpoints such as progression-free survival are evaluated as patient-relevant[8, 9]. Formally, it differs, among other things, in that there are five categories, no „additional benefit not quantifiable" category, and different scales for pharmaceuticals in indications with curative and non-curative intent. Figure 8 shows the evaluation of 90 consecutive oncology procedures in non-curative intent, in which results of the early benefit assessment and evaluation ac-

Best assessment by procedure and subgroups in the early benefit assessment, all specialties 2011 to 2020



Key: Best assessment – in procedures with subgrouping, the best assessment in each case is evaluated; in procedures without subgrouping, the only determination in each case is evaluated; all subgroups/subpopulations – the determinations of all subgroups are evaluated here.

Source: AWMF and DGHO: Early benefit assessment of new pharmaceuticals in Germany 2011-2020, pricing and more. May 2021, in print.

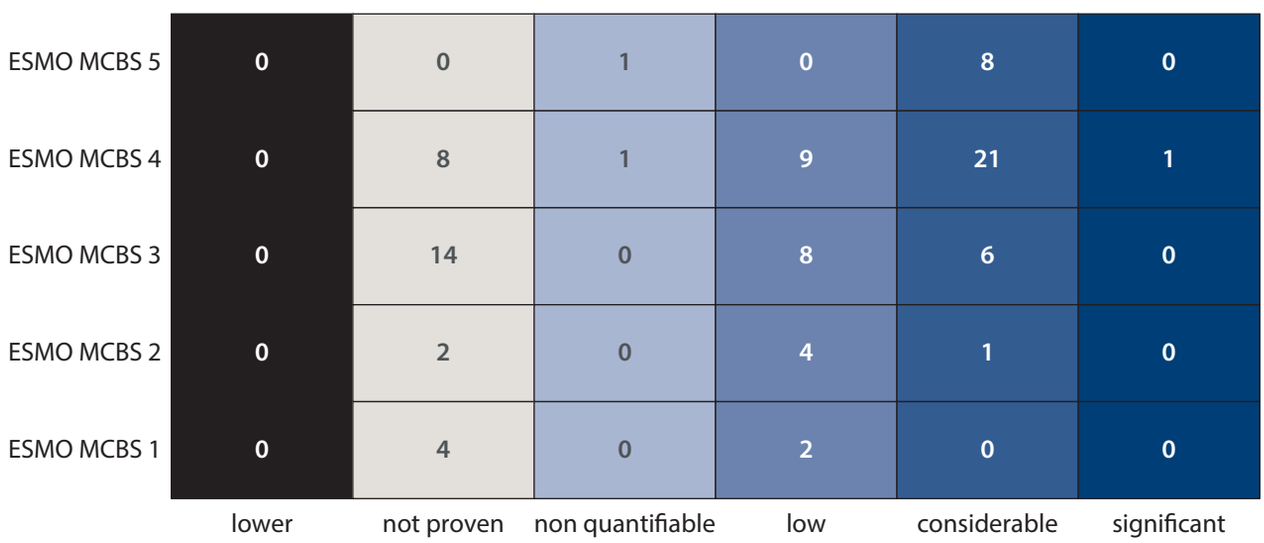
Figure 7: The results from 519 AMNOG procedures and 966 determinations show that in 41.1% of all cases the assessment resulted in „additional benefit not proven." In the evaluation of subgroups, this was the case in 59.6% of the cases.

cording to the ESMO MCBS were available. There is a tendency that the results of AMNOG and ESMO MCBS procedures match, but within the respective categories the results show a wide range of variation. One example is the AMNOG category „low additional benefit", in which ESMO ratings range from 1-4.

Early integration of medical societies in the consultation processes

One important element in optimising HTA processes is an early communication between pharmaceutical companies and the G-BA. With the GSAV of August 2019, medical societies have now also been involved in this consultation[3].

Comparison of the assessment according to AMNOG and ESMO. (ESMO-MCBS: Magnitude of clinical benefit according to the scale of the European Society for Medical Oncology)



Source: Prof Dr Wörmann

Figure 8: When comparing 90 assessments according to AMNOG and ESMO MCBS for oncology pharmaceuticals with non-curative intent, the results vary greatly within the categories.

This law has been implemented since spring 2020. In a working paper for the AWMF, the medical societies have agreed to issue a joint statement. The AWMF office sends the consented statement to the G-BA or one of its commissioned medical societies within a period of four to five weeks. Table 1 shows all requests sent by the G-BA from April to December 2020.

This procedure is quite complex for the medical societies. The initial time required for a statement is estimated up to one working day. Against the background of this effort, the compliance rate of 85% for all specialties is very high, especially as the implementation of this procedure fell directly into the first wave of COVID-19 in Germany.

References

[1] Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (Arzneimittelmarkneuordnungsgesetz – AMNOG), Bundesgesetzblatt Teil I vom 27. 12. 2010. https://go.sn.pub/nUgQBj

[2] Gesetz zur Stärkung der Arzneimittelversorgung in der GKV (GKV-Arzneimittel- versorgungsstärkungsgesetz - AMVSG), 2017 https://go.sn.pub/Y13TDn

[3] Gesetz für mehr Sicherheit in der Arzneimittelversorgung, 2019. https://go.sn.pub/hGq5QK

[4] AWMF und DGHO: Frühe Nutzenbewertung neuer Arzneimittel in Deutschland 2011-2020, Preisbildung und mehr. Mai 2021, im Druck.

[5] https://go.sn.pub/d8pvSg

[6] Frühe Nutzenbewertung neuer Arzneimittel in Deutschland - Subgruppen Definition, Analyse und Kriterienkatalog, 2016. https://go.sn.pub/Nz4ulO

[7] LSG Berlin Brandenburg Az.: L 9 KR 72/16 KL vom 28.06.2017.

Early involvement of medical societies in the consultations of the G-BA (4-12/2020)

Indications	N	Opinions
All	224	191 (85%)
Oncology	104	101 (97%)
Non-oncology	120	90 (75%)

Source: Prof Dr Wörmann

Table 1: Participation of medical societies, as measured by G-BA requests, reaches an average of 85%, and 97% in the specialty of oncology, respectively.

[8] Cherny NI, Sullivan R, Dafni U et al.: A standardised, generic, validated ap- proach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-1573, 2015. DOI: 10.1093/annonc/mdv249. https://go.sn.pub/UNSQmu

[9] Cherny NI, Dafni U, Bogaerts J et al.: ESMO-Magnitude of Clinical Benefit Scale version1.1. Ann Oncol 28:2340-2366, 2017. DOI: 10.1093/annonc/mdx310. https://go.sn.pub/3eRv86

General practice and the AMNOG: the status quo

Professor Martin Scherer, Institute and Polyclinic for General Medicine UKE Hamburg, President of DEGAM | Professor Erika Baum, Treasurer and Past-President of DEGAM

In the AMNOG procedure, the benefit of new treatment methods is evaluated. For this purpose, the assessment of scientific professional associations is also required at several stages. This article illustrates the role of general practice in this process. We explain why the involvement of this discipline is essential and represents an important corrective, where there are similarities and discrepancies, and how this should be rated. In particular, we refer to the close connection between guidelines and the information provided in the AMNOG procedure. It becomes apparent that the coordinating function of the AWMF is extremely useful. This applies to both benefit assessment and guideline development – in both areas we see ourselves as learning systems.

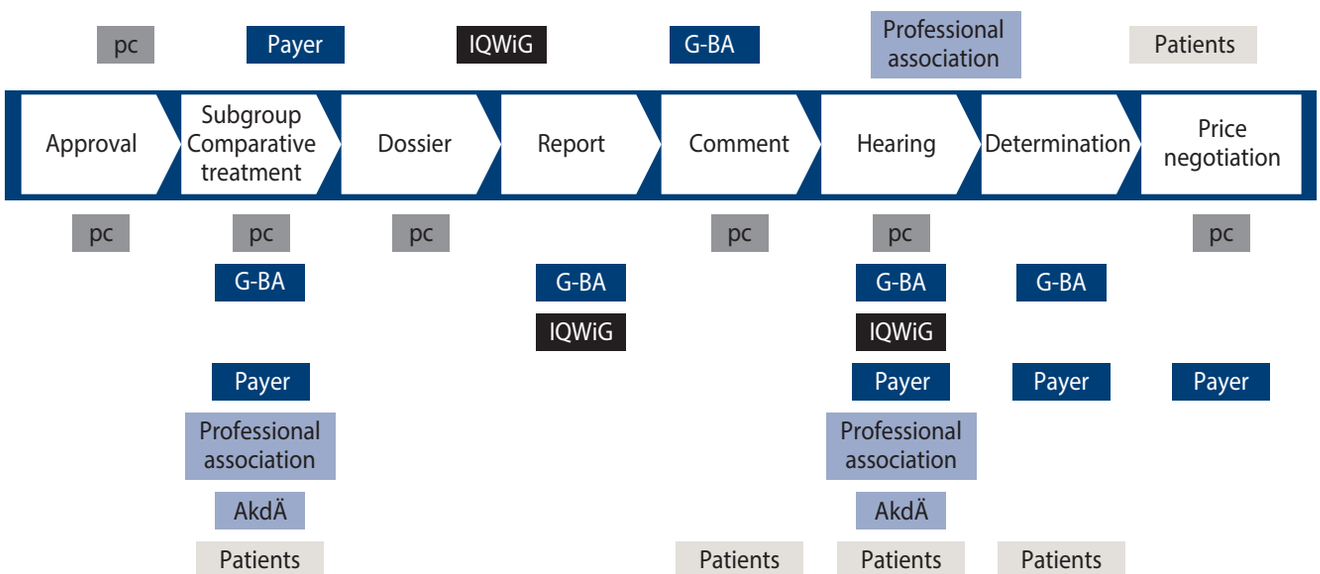
Process flows

Last year, the AMNOG procedure was expanded and a consultation phase implemented. In the so-called „report" phase, the AWMF professional associations are asked for a brief statement about the current treatment standard and the actual medical care situation. Since general practice cares for people with a wide variety of diseases, DEGAM is frequently involved in the hearing procedure (see figure 1). In addition to DEGAM, the coordinator of the AWMF, Ms Erstling, also contacts the main authors of relevant guidelines. Several inquiries reach DEGAM activists via this channel. In the commission „Early benefit assessment", Professor Erika Baum who looks back on 36 years of experience in a rural family practice and is the former DEGAM president and head of the department of general medicine at the University of Marburg, assumes the coordination function for DEGAM. She is supported by Dr Felix Holzinger from the Institute of General Practice at the Charité Berlin. Since a joint statement of all AWMF specialist societies is expected, the challenge is that partially different assessments and views must be combined here within only a few weeks.

Special position of general medicin

It is no coincidence that DEGAM frequently comes to different assessments of diagnostic and therapeutic procedures than the other professional associations. General medicine focuses on the whole person and on the question of practicability under the given conditions. Our main focus is on the overall benefit for our patients: How does a certain procedure affect mortality – and not just disease-specific mortality, because we always have to take competing causes of death into account – morbidity in the sense of the burden of disease, and especially quality of life. Moreover, opportunity costs play a major role: We can only spend

Overview of the AMNOG procedure



Source: Prof Wörmann, AWMF

Figure 1: Due to the tight time frame of the AMNOG process, a statement must be submitted within a few weeks.

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Professor Erika Baum *studied medicine in Gießen. She is a specialist in general medicine and worked as a research assistant in the professorship for general medicine in Gießen. Since 1990, she holds a professorship for general medicine at the University of Marburg and also works in a general practice in Biebertal near Giessen. From 2010, Vice President and from 2016 to 2019 President of DEGAM. Since 2019, Treasurer of DEGAM.*

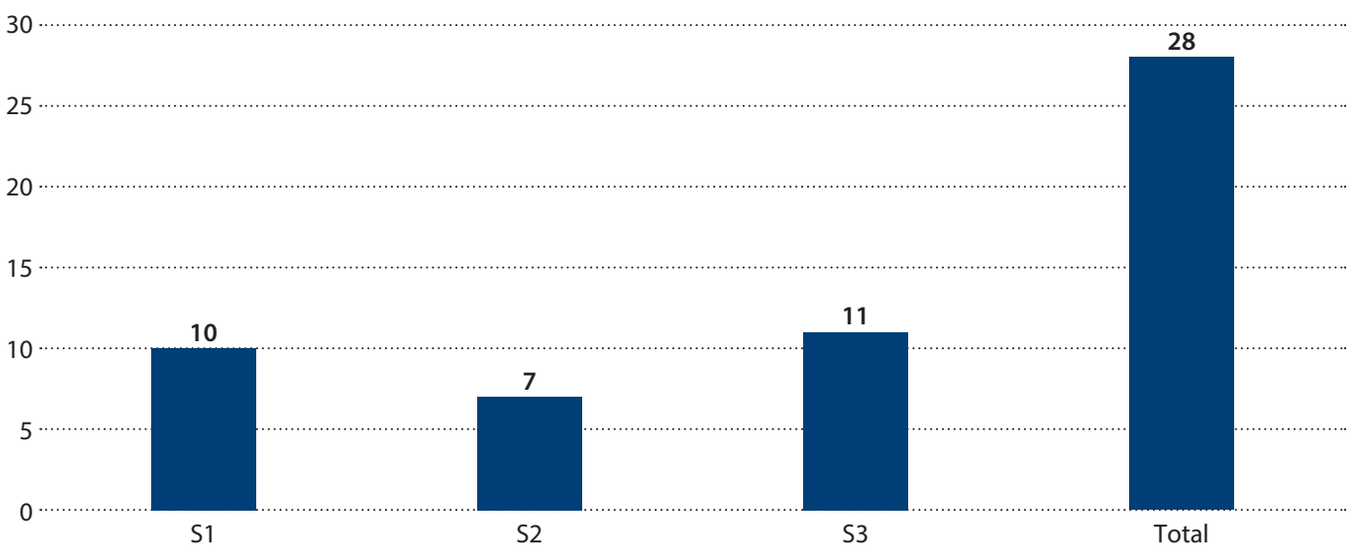
one Euro and allocate one minute of our working time once. Thus, the question of displacement and cost-benefit ratio also arises in comparison to other diseases and the burden on the overall system[1].

Traditionally, DEGAM pays great attention to its independence from the pharmaceutical and medical device industry. We have this in common with the Drug Commission of the German Medical Association (Arzneimittelkommission der Deutschen Ärzteschaft, AKdÄ). Contrary to most other professional associations in Germany, we refrain from any sponsorship by these groups – both as a society and in our journal and at our congresses. Our guideline authors and delegates to external guidelines are also free of any potential conflicts of interest. Since they play a considerable role in the evaluation of therapeutic and diagnostic procedures[2], it is no coincidence that repeatedly, e.g. in national health care guidelines, DEGAM and AKdÄ have voted in the same way and controversially to the other professional associations. In the opinion of DEGAM, in guideline work too little attention is paid to the bias caused by the underlying publications as a result of potential conflicts of interest on the part of their authors[3].

DEGAM puts a lot of effort into writing high-quality and trustworthy guidelines that are easy to apply in family practice. The guidelines including their additional materials such as abstracts and implementation tools are available at https://www.degam.de/degam-leitlinien-379.html. Moreover, we are involved in guidelines of numerous other

Number and type of guidelines developed by DEGAM until September 2020

Status: September 2020



Source: DEGAM

Figure 2: By autumn 2020, DEGAM has developed a total of 28 guidelines, including eleven S3 guidelines.

professional societies as well as in the programme of national health care guidelines: https://www.degam.de/nvls3-ll-anderer-fg.html. Unfortunately, due to limited human and financial resources, DEGAM must reject quite a few requests from other professional associations.

Implementation in the AMNOG procedure

These fundamental views and problems are also reflected in the joint statements. For example, consensus on request 2021-B-059_AWG2 – Prevention of SARS-CoV-2 infections or COVID-19 diseases was quite easy. We shared the opinion of the representatives of other professional associations (German Society for Internal Intensive Care and Emergency Medicine and German Society for Pneumology and Respiratory Medicine) concerning the insufficient evidence base and the much discussed options antibiotics, hydroxychloroquine, monoclonal antibodies, and vitamin D. Regarding vaccinations, we referred to the STIKO recommendations. Especially in this case, evidence is so volatile that our consensus is that one should always refer to the current status published by this public institution.

In contrast, there was a disagreement in the assessment of the significance of direct oral anticoagulants (DOAC) versus vitamin K antagonists in atrial fibrillation. While the other professional associations referred to international guidelines and global results of randomised studies, DEGAM found it important to take the assessment of the AKdÄ into consideration (available at https://www.akdae.de/Arzneimitteltherapie/LF/OAKVHF/index.html) as well as the S3 Guideline Stroke, which was prepared under the leadership of DEGAM. In particular, a more detailed analysis of the data shows that the phenprocoumon therapy commonly used in Germany (instead of warfarin, which is otherwise used almost exclusively) and the treatment quality achieved do not present any systematic disadvantage as compared to DOACs.

Our ongoing dispute regarding the evaluation of lipid-lowering therapy has also been part of these hearing procedures, as we had expected it. Initially, there were even separate statements, and later the different views were presented; in one case, DEGAM explicitly distanced itself from the statement issued, because it had been involved too late by the lead professional association. We are quite disappointed that in the comments of other professional associations our nationally consented National Health Care Guidelines (NVL), which had been elaborated with the participation of the AWMF at the highest level and are ultimately financed by German medical profession, are often not reflected at all, but instead guidelines from professional societies are cited, such as the European Society of Cardiology (ESC), that do not reach this standard by far[4].

In case of antidementive pharmaceuticals, we objected to the assertion that substandard therapy was applied in general practice. Instead, we referred to the special vote of DEGAM in the corresponding national guideline, to the specifications of the German Pharmaceuticals Guidelines for these pharmaceuticals[5], which the lead professional association wasn't obviously aware of at all, as well as to the new development in France, where antidementives were excluded from reimbursability for reasons of insufficient efficacy[6].

These different views and representations are not a problem for us, but serve the purpose of transparency. We have different treatment areas, different pretest probabilities, different positive or negative predictive values based on different prevalences. We also have different perceptions related to the importance of interventions and what is ultimately really urgent and realistic and achievable.

Therefore, it is very important that general practice is heard and actively involved within the AWMF. Unlike many

other professional associations, we are not divided into subgroups with our own representation within the AWMF. We are grateful that this special role of general practice represented by DEGAM is taken into account in the hearing procedure as well as in the guideline work.

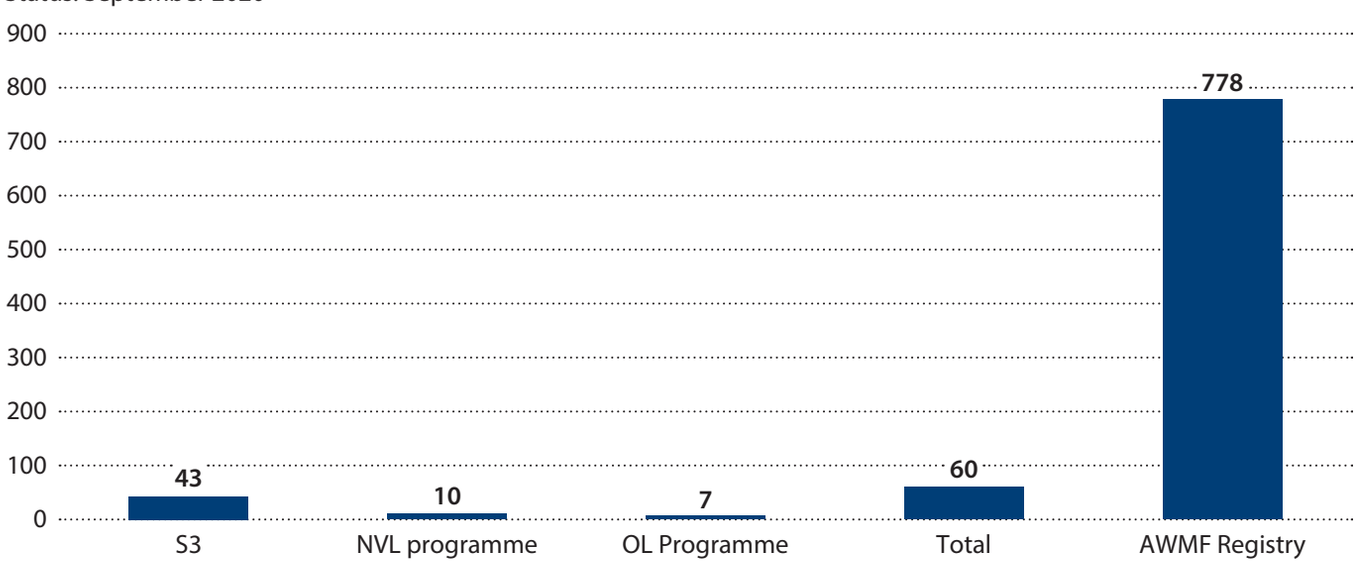
Notes on the development of guidelines

Finally, we would like to mention the guideline work of DEGAM. Our challenge here is to combine scientific expertise with clinical practice. In view of the time-consuming development process starting at S2 level, it is very difficult for us to find suitable people who are willing and able to do the – usually voluntary – work for this. There is hardly any additional support or funding. We hope that the situation will improve with the commitment by the Innovation Fund to support guideline work. A special programme for the field of general practice would be very helpful. But there is also a considerable catch-up potential in terms of guideline implementation (see figure 4).

What we need to communicate again and again: Guidelines are not textbooks; as we are not into cookbook medicine. The implementation of guidelines in the sense of changing the behaviour of physicians and patients is quite challenging, as we also write patient information. We have

Overview of DEGAM's collaboration on guidelines

Status: September 2020



NVL: National health care guideline; OL: Guideline programme oncology

Source: DEGAM

Figure 3: By autumn 2020, DEGAM has contributed to a total of 60 guidelines, including 43 S3 guidelines, ten national care guidelines and seven from the guideline programme oncology.

various tools: a long version, a short version, several implementation aids for medical assistants, and other supplementary materials for practices, such as medical history forms. And at present, with COVID-19 and the rapidly changing evidence, we need a living guideline including patient guides and modules for various individual scenarios, such as specimen collection, self-testing, or home isolation.

Guidelines also help transfer evidence into practice via the appropriate recommendations. But they need to be done well. For this purpose, we have the DELBI criteria (German Instrument for Methodological Guideline Evaluation) and the AGREE criteria[7] (Appraisal of Guidelines of Research & Evaluation). Of course, guidelines must always be measured by their impact on health care. Health care issues also always play a role in the development of a guideline, we don't write a book on dementia or on stroke or an encyclopaedia. Instead, we must always adapt the guideline to current health care issues. In doing so, we see ourselves as a learning system. Basically, the cycles from health care problem to the implementation of a quality-improving measure are learning systems driven by iterative feedback loops.

And it is also about recurrent feedback loops. A sensitive breaking point is ensuring continuity at expert level and taking care not to overburden people who do this work on a voluntary basis. Often less is more. For this reason, we try to be brief and get to the core of the matter in the various commenting procedures, even outside the AMNOG. Through concise core messages, people in primary care get aware of us and can actually change their behaviour and achieve ever-improving medical care for our country.

Obstacles in the implementation of guidelines

Source: AWMF

Figure 4: There are several barriers to guideline implementation in terms of behavioural change.

References

[1] https://go.sn.pub/uoux7S besucht am 11.5.2021.

[2] Lundh A , Lexchin J , Mintzes B , Schroll JB, Bero L: Industry sponsorship and research outcome. Cochrane Database Syst Rev 2017 Feb 16;2:MR000033. doi: 10.1002/14651858.MR000033.pub3. https://go.sn.pub/u7mDNk

[3] Ahn R, Woodbridge A, Abraham A, Saba S, Korenstein D, Madden E, Boscardin WJ, Keyhani S: Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study BMJ 2017; 356 doi: https://doi.org/10.1136/bmj.i6770. https://go.sn.pub/2AO6da

[4] https://go.sn.pub/HMx3Ex letzter Absatz besucht am 11.5.2021.

[5] Arzneimittelrichtlinie Anlage III: https://go.sn.pub/GFYtqd Punkt 10 Seite 10, besucht am 3.2.2021.

[6] https://go.sn.pub/JmHWej (letzter Zugriff: 02.02.2021).

[7] https://go.sn.pub/P7R061

Experiences of psychiatry/neurology with early benefit assessment

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Mental disorders are very common and too rarely treated. Functional remission rates are low (15 to 50 percent) and the patients' life shortened (3-10 years). There are still hardly any new pharmacological approaches. The AMNOG requires an additional benefit, while the choice of an appropriate comparative treatment is often difficult to define despite existing guidelines. New therapeutic approaches must focus on potential subgroups and relevant endpoints. Mechanism-based therapeutic approaches or (bio)-marker-guided studies are the future and must be adapted to current needs.

1 Mental disorders – prevalence, treatment rate, outcome, costs

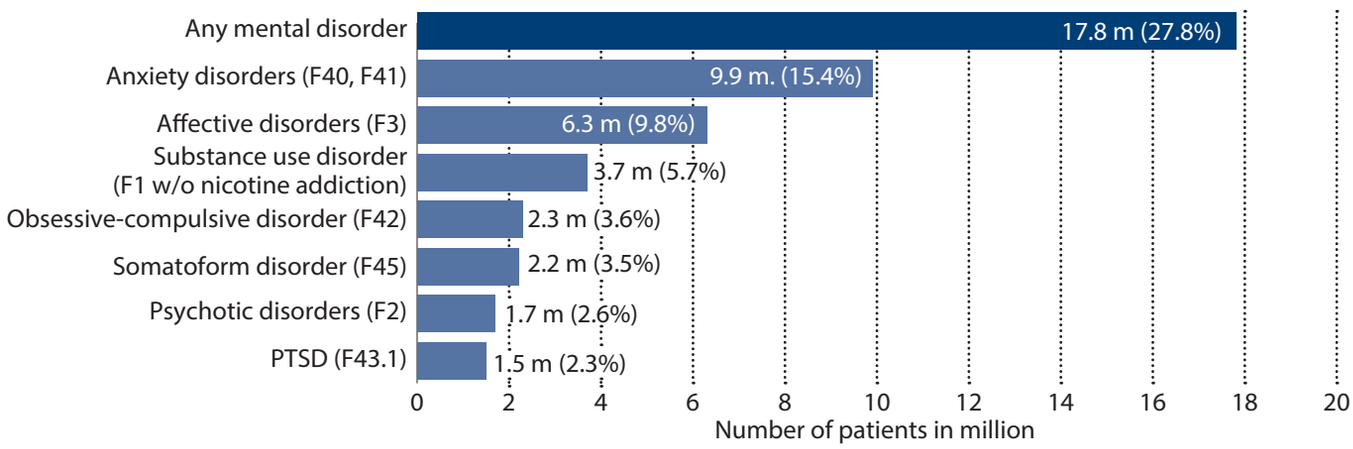
27.8 percent of the German population (17.8 million inhabitants) suffer from a mental disorders (figure 1) and of these, 9.8 percent (6.3 million) suffer from depression[1].

This group of disorders is the second most common after anxiety disorders. It is characterised by disease episodes in which mood and drive are significantly decreased below previously known levels for a period of at least 14 days. Patients usually suffer from depression for months to years before it is recognised. Only 32.9 percent of all cases are treated although there are good treatment options ranging from a psychotherapy-only treatment recommendation for a mild episode to a combined treatment of pharmacotherapy and psychotherapy for a severe episode[2].

Approximately 50 percent of all patients treated respond very well to evidence-based treatment options and are able to return to life without significant impairment. The other half lives well with disease-related limitations, but some patients develop chronic courses. These are characterised by significant concentration disorders as well as severe impairment of both vitality and mood, which do not respond to current psycho- or pharmacotherapy options, and are associated with significant limitations in both professional and private life.

Unfortunately, new treatment options, such as the administration of esketamine or the use of non-invasive brain stimulation (NIBS) have not changed much yet. Depression is currently one of the main drivers of rising absenteeism and work disability rates (figure 2) due to mental disorders[3]. With 13 percent of total costs, they contribute significantly to the 44.4 billion € of direct medical and healthcare costs in Germany (figure 3)[4]. At the same time, however, new pharmacological approaches are becoming increa-

People in Germany suffering from a mental disorder



Source: German Psychotherapists Association (Deutsche Psychotherapeuten Vereinigung e.V.. 2020): Report Psychotherapy 2020.

Figure 1: Almost 28 percent of all people in Germany suffer from a mental disorder, of which almost ten million have an anxiety disorder. Around 6.3 million people suffer from depression.

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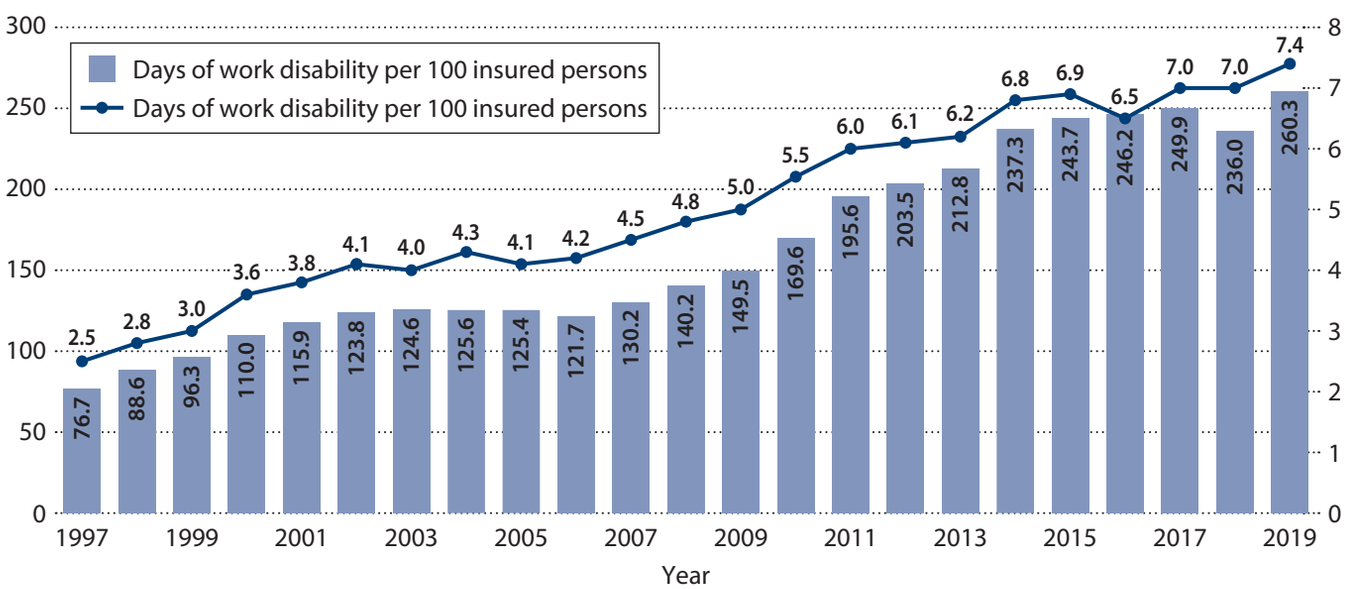
Anja Dorothée Streb, M.A., *graduated from the German School Tokyo in 1989. After her studies of the Japanese and English language and literature she became consultant at the Department of Psychiatry and Psychotherapy, LMU Munich, in 2008 and is responsible for coordination and editorial work on scientific matters.*

PD Dr. Cornelius Schüle, *studied human medicine at the Rupprecht-Karls-University Heidelberg and received his doctorate in 2001 at the LMU Munich. After his further training as a specialist in psychiatry and psychotherapy, he started working as senior physician at the Psychiatric Clinic of the LMU in 2009 where he is – among other things – responsible for the depression ward.*

Mental diseases reach peak



Source: https://www.dak.de/dak/download/190725-pm-psychoreport-pdf-2125480.pdf

Figure 2: Depressive diseases are a significant cause of increasing days of work disability. The days of work disability reached a new high in 2019 with 260 days per 100 insured persons.

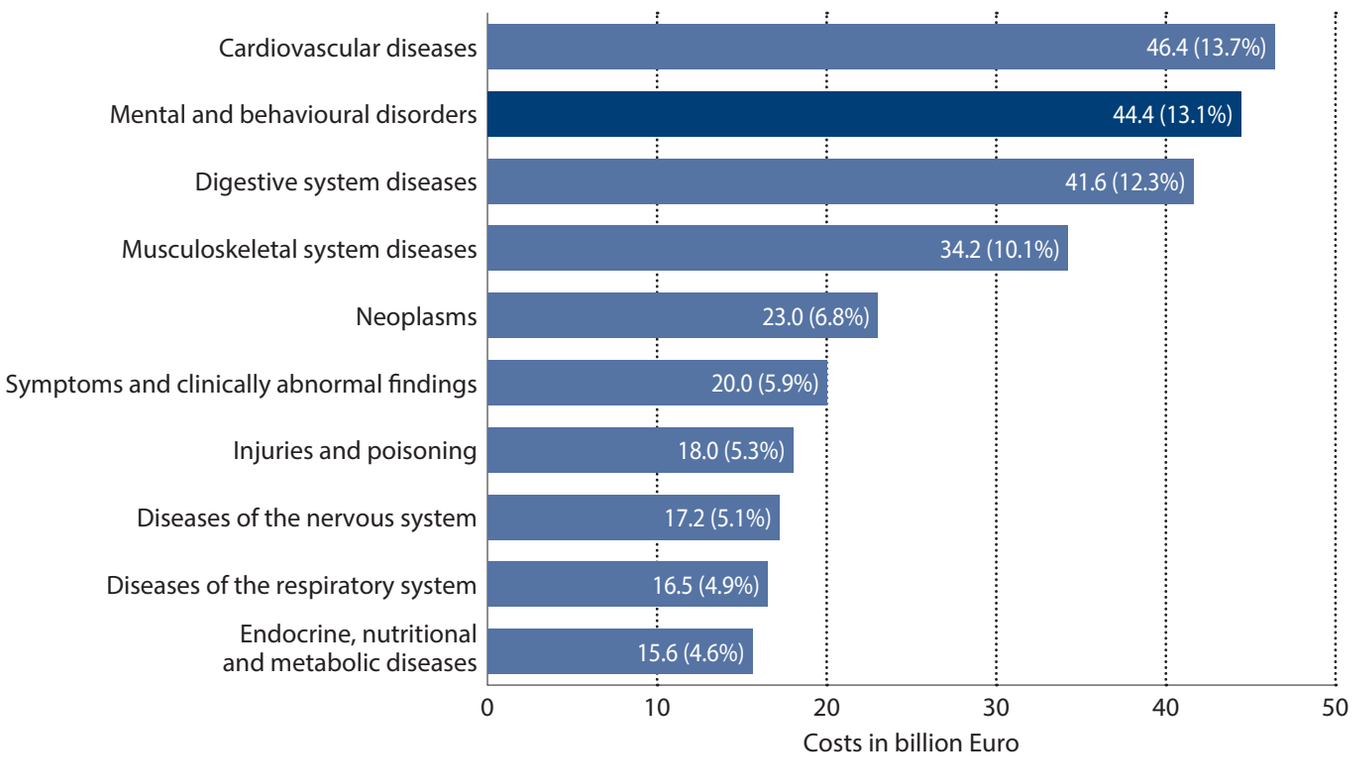
singly rare, as the pharmaceutical industry's interest in developing new drugs for mental disorders has noticeably declined in recent years.

2. The AMNOG procedure

With the adoption of the German Pharmaceutical Market Reorganisation Act (AMNOG) in January 2011, the previously applicable bonus-malus system for the prescription of pharmaceuticals was abolished. The basis for the bonus-malus system was the Economic Optimisation of Pharmaceutical Care Act (AVWG) which came into force in 2006. This regulation provided for penalties for physicians, if they exceeded the specified daily therapy costs for certain diseases (malus). In contrast, there was a bonus for the Association of Statutory Health Insurance Physicians, if physicians prescribed particularly favourable alternative pharmaceuticals and smaller dosages. The calculation of daily therapy costs was based on pharmaceuticals in the lower third of the price range and an assumed mean daily dose (MDD).

In all of this, individual characteristics, the severity of the disease and existing comorbidities were not taken into account. In addition, the rewarding of rationing of medical services and an increasing breach of the relationship of trust between physician and patient were frequently criticised. The pharmaceutical industry was blamed for the tremendous increase in expenditure on new pharmaceuticals,

Direct costs in Germany – the most common diseases



Source: German Psychotherapists Association (Deutsche Psychotherapeuten Vereinigung e.V.. 2020): Report Psychotherapy 2020.

Figure 3: The direct costs of mental disorders in Germany most recently added up to around 44.4 billion € annually – almost as much as the costs of cardiovascular diseases.

as manufacturers were able to set the price for new pharmaceuticals – and high prices were by no means always justified by a high additional benefit for patients.

The goals of the AMNOG are 1) to contain the rapidly increasing pharmaceutical expenditures of statutory health insurances (SHI), 2) to promote fair competition and a stronger focus on the well-being of patients, 3) to achieve a new balance between innovation and affordability of pharmaceuticals, 4) to determine a price based on the additional benefits of pharmaceuticals, and 5) to better inform patients by means of independent patient counselling.

The desired consequences of the AMNOG are, on the one hand, annual savings for the statutory health insurance and, on the other hand, more competition. It is no longer the pharmaceutical companies' sole discretion to set the prices for pharmaceuticals. Moreover, the reimbursement amount is now negotiated between pharmaceutical

manufacturers and the statutory health insurances within one year of market launch. This amount also applies to privately insured and self-pay patients. Other goals include deregulation through AMNOG by abolishing the bonus-malus system as well as the second opinion regulation (high-priced pharmaceuticals or those with a high risk potential may not be prescribed without feedback from another physician), and reducing bureaucracy for insured persons and service providers.

The Federal Joint Committee (G-BA) is the highest body of the joint self-government in Germany's healthcare system and is mandated by law to make legally binding decisions in many areas about the entitlement to benefits of the community of solidarity of around 70 million people insured under the SHI in Germany. It examines whether services provided by the statutory health insurance (SHI) are „sufficient, appropriate and economical" (pursuant to Section 12 of the German Social Code – Book V (SGB V), they must „not exceed what is necessary" (efficiency principle)). The G-BA issues directives, such as the German Medical Aids Directive (HilfsM-RL), the Physiotherapy Directive (HeilM-RL), and the Pharmaceutical Products Directive (AM-RL).

Despite their „sub-legal normative character", the guidelines of the G-BA are legally binding for all people insured and stakeholders in the SHI system (e.g., for outpatient treatment by physicians, dentists, therapists and psychotherapists in private practice, as well as for treatment in hospitals and clinics). These are only formal, yet not substantive, reviews by the Federal Ministry of Health. The Committee is supported by the Institute for Quality and Efficiency in Health Care (IQWiG) by means of expert opinions.

3. Examples for the application of the AMNOG procedure/appropriate comparative treatment

- Vortioxetine (Brintellix®): no additional benefit in acute therapy as well as in relapse prophylaxis of depression;
- Lurasidone (Latuda®): no additional benefit in acute therapy and relapse prophylaxis of schizophrenia;
- Nalmefene (Selincro®): additional benefit of nalmefene in the reduction of alcohol consumption as compared to the appropriate comparator therapy not proven;
- Lisdexamfetamine (Elvanse®): approval for ADHD in children and adolescents aged six years and older with an inadequate response to therapy with methylphenidate; additional benefit as compared to atomoxetine not proven;
- Cariprazine (Reagila®): Additional benefit only for the treatment of negative schizophrenia symptoms, calculation of a mixed price (avoidance of additional costs in the treatment of productive symptoms).

In the AMNOG procedure, the G-BA – with the involvement of IQWiG – did not recognise an additional benefit of e.g. vortioxetine (Brintellix®). Thus, the pharmaceutical remains to be approved, but is not reimbursed at the price sought by the pharmaceutical company. As a consequence, it was de facto withdrawn from the German market. The criticism: Only acute therapy was tested, there were no studies on the subgroup of mild episodes, and for severe depressive episodes there was a comparison with citalopram without any consideration of psychotherapy. Although meta-analyses (for lack of directly comparative studies) identified 14 studies with vortioxetine and 10 with citalopram, only three and four of these studies were included, respectively. Vortioxetine (Brintellix®) was approved, but only a very low market price was achieved, equivalent to the reimbursement costs of Fevarin®, a selective serotonin reuptake inhibitor (SSRI) that had been approved a long time ago. The manufacturer withdrew vortioxetine (Brintellix®) from the

market in Germany, as other European countries would have been able to obtain this pharmaceutical very cheaply in Germany.

With regard to nalmefene (Selincro®), naltrexone was intended to serve as an appropriate comparative treatment for relapse prevention of alcoholism. In IQWiG's view, the data presented by the manufacturer were unsuitable to demonstrate an additional benefit. They only allowed an indirect comparison between nalmefene and naltrexone, which was also associated with the methodological shortcomings that patients and treatment goals differed fundamentally in six of seven studies on naltrexone from those in the nalmefene studies, in the seventh study naltrexone was sometimes not used in accordance with the approval, and evaluations for relevant time periods were missing in the study.

For cariprazine (Reagila®), the G-BA did not see any additional benefit in the acute treatment of schizophrenia in adults as compared to an appropriate comparative treatment on the basis of the available studies. However, one controlled study revealed a „small but robust effect on negative symptoms" of cariprazine in schizophrenic patients that showed statistically significant superior results as compared to the effects of risperidone. Thus, the G-BA saw at least „evidence of additional benefit" in schizophrenic patients in whom negative symptoms predominate, whereby the additional benefit was mainly seen in the long-term treatment and relapse prevention of schizophrenia.

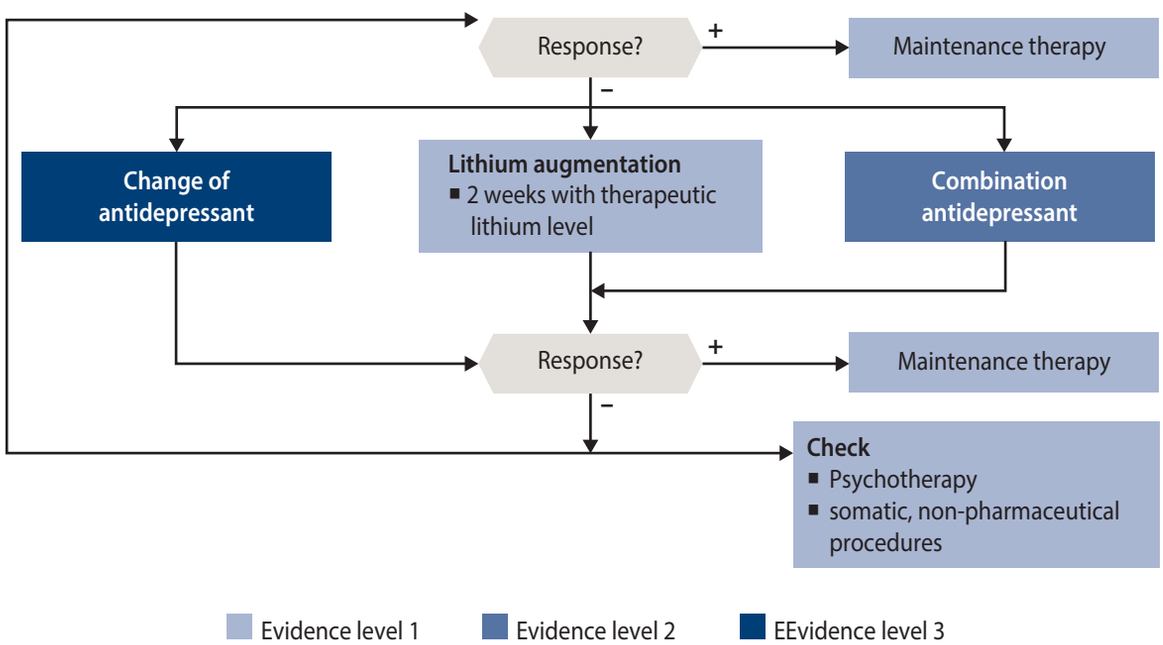
Before the introduction of the AMNOG procedure, a comparable effect as compared to a standard therapy and superiority over placebo was deemed sufficient to furnish proof of efficacy to allow for approval and increased reimbursement costs for the new pharmaceutical within the scope of patent protection, and the manufacturer was ultimately able to determine the price for the pharmaceutical. After the introduction of the AMNOG procedure, a comparable effect as compared to an already established standard therapy and superiority over placebo is no longer sufficient; proof of an additional benefit is required in order to be able to justify an increased market price for the newly approved pharmaceutical, while a verifiable additional benefit of the new pharmaceutical has a direct influence on the price negotiations between the manufacturer and the statutory health insurances.

On the example of pharmacotherapy for depressive patients, the extent to which superiority can be demonstrated for a new therapeutic strategy as compared to an appropriate comparative treatment will be explained once again. According to the guidelines, the algorithm for antidepressant pharmacotherapy mentions three options in case of insufficient treatment response (figure 4):

- Change of the antidepressant;
- Augmentation (additional administration of a pharmaceutical that is not antidepressant alone, but also enhances the effect of an antidepressant);
- Combination (additional administration of another antidepressant).

On the one hand, it is remarkable that the augmentation strategy is assigned the highest level of evidence even before the combination strategy and that the change of antidepressant is less supported by empirical studies. On the other hand, among the augmentation strategies, lithium is singled out in first place, even though other augmentation methods (e.g., augmentation with thyroid hormone or atypical antipsychotics, such as quetiapine or aripiprazole) might have yielded even better results than lithium in meta-analyses (figure 5). Regarding the role of the G-BA and appropriate comparative treatment in the approval of augmentation procedures, the G-BA – as opposed to the DGPPN guideline – does not „rank" therapy options in pati-

Antidepressant pharmacotherapy for inadequate response



Source: Bschor T, Bauer M, Adli M (2014): Chronic and treatment resistant depression: diagnosis and stepwise therapy. Dtsch Ärztebl Int 111: 766–776.

Figure 4: According to the guidelines, the algorithm for antidepressant pharmacotherapy mentions three options in case of insufficient treatment response.

ents with treatment-resistant depression (TRD). In principle, potential appropriate comparative treatments would be 1) a change of the pharmaceutical (with a change of the substance class), 2) combination strategies, or 3) augmentation strategies.

With regard to augmentation strategies as appropriate comparative treatment, the following applies:

- Lithium: mentioned in the DGPPN guideline with the highest evidence, for augmentation in TRD, therefore according to G-BA appropriate comparative treatment;
- Augmentation with thyroid hormone: no approval as augmentation strategy in TRD, therefore according to G-BA no appropriate comparative treatment;
- Qetiapine: approved as augmentation strategy in TRD, therefore appropriate comparative treatment according to G-BA;
- Aripiprazole: approved in the USA as an augmentation strategy for TRD (but not in Europe), therefore not an appropriate comparative treatment according to the G-BA.

For the most recent launch of intranasal esketamine (Spravato®) in Germany (1 March 2021), a switch of antidepres-

Meta-analysis of various augmentation procedures

ARI	1.61 (0.54–4.18)	1.39 (0.48–3.54)	1.93 (0.53–5.17)	1.16 (0.42–2.72)	1.29 (0.31–3.72)	1.23 (0.49–2.74)	3.79 (0.43–15.28)	1.46 (0.62–3.33)	1.18 (0.43–2.82)	3.84 (0.75–12.82)	1.24 (0.72–2.41)
1.49 (0.70–2.66)	**BUP**	0.94 (0.39–1.98)	1.42 (0.32–3.92)	0.84 (0.25–2.07)	0.95 (0.19–2.81)	0.90 (0.28–2.10)	2.79 (0.27–11.56)	1.07 (0.37–2.51)	0.85 (0.27–1.99)	2.72 (0.51–8.92)	0.85 (0.39–1.97)
1.53 (0.76–2.59)	1.08 (0.60–1.73)	**BUS**	1.64 (0.38–4.43)	0.97 (0.30–2.28)	1.09 (0.22–3.15)	1.04 (0.33–2.32)	3.21 (0.32–13.28)	1.22 (0.43–2.74)	0.96 (0.34–2.09)	3.04 (0.65–9.27)	0.99 (0.46–2.22)
1.71 (0.66–3.59)	1.24 (0.44–2.80)	1.19 (0.44–2.61)	**LAM**	0.74 (0.21–1.97)	0.85 (0.15–2.76)	0.81 (0.22–2.15)	2.49 (0.23–10.76)	0.95 (0.28–2.55)	0.78 (0.20–2.18)	2.51 (0.37–9.24)	0.70 (0.30–2.06)
1.23 (0.62–2.04)	0.89 (0.41–1.61)	0.84 (0.44–1.47)	0.82 (0.33–1.70)	**LIT**	1.26 (0.28–3.61)	1.21 (0.43–2.66)	3.73 (0.40–15.28)	1.37 (0.65–2.70)	1.15 (0.38–2.71)	3.70 (0.71–12.10)	1.18 (0.61–2.46)
1.39 (0.56–2.78)	1.01 (0.38–2.19)	0.96 (0.38–2.04)	0.95 (0.29–2.30)	1.19 (0.49–2.51)	**MPD**	1.29 (0.31–3.64)	3.98 (0.32–17.58)	1.53 (0.39–4.39)	1.24 (0.28–3.69)	4.03 (0.54–15.31)	1.06 (0.42–3.60)
1.37 (0.71–2.25)	0.99 (0.46–1.84)	0.95 (0.48–1.70)	0.93 (0.36–2.03)	1.17 (0.62–2.07)	1.11 (0.45–2.30)	**OLZ**	3.37 (0.38–13.60)	1.29 (0.55–2.80)	1.05 (0.38–2.41)	3.41 (0.66–11.20)	1.11 (0.62–2.07)
2.00 (0.73–4.35)	1.45 (0.49–3.33)	1.38 (0.51–3.04)	1.35 (0.39–3.44)	1.71 (0.63–3.89)	1.63 (0.49–4.06)	1.53 (0.56–3.41)	**PDL**	0.81 (0.09–3.16)	0.66 (0.07–2.61)	2.14 (0.14–9.92)	0.36 (0.09–2.71)
1.00 (0.50–1.58)	0.72 (0.33–1.26)	0.68 (0.35–1.15)	0.67 (0.26–1.41)	0.83 (0.51–1.26)	0.81 (0.33–1.61)	0.76 (0.40–1.24)	0.59 (0.21–1.26)	**QTP**	0.87 (0.32–1.88)	2.83 (0.56–9.06)	0.94 (0.52–1.63)
1.29 (0.65–2.24)	0.93 (0.44–1.77)	0.88 (0.46–1.58)	0.87 (0.32–1.94)	1.10 (0.56–2.02)	1.05 (0.41–2.27)	0.99 (0.50–1.81)	0.76 (0.27–1.72)	1.35 (0.72–2.51)	**RIS**	3.48 (0.78–10.58)	1.15 (0.59–2.46)
1.04 (0.47–1.97)	0.75 (0.32–1.50)	0.71 (0.34–1.34)	0.70 (0.24–1.63)	0.87 (0.45–1.59)	0.85 (0.30–1.92)	0.80 (0.36–1.57)	0.61 (0.20–1.47)	1.09 (0.53–2.08)	0.85 (0.40–1.59)	**THY**	0.36 (0.12–1.51)
1.85 (1.27–2.72)	1.29 (0.78–2.34)	1.25 (0.82–2.12)	1.12 (0.57–2.59)	**1.56 (1.05–2.55)**	1.37 (0.74–2.99)	1.40 (0.96–2.24)	0.96 (0.47–2.33)	**1.92 (1.39–3.13)**	1.49 (0.94–2.51)	**1.84 (1.06–3.56)**	**PBO**

Treatment Response rate, OR (95% CrI) All-cause discontinuation, OR (95% CrI)

[a] Drugs are reported in alphabetical order. Comparisons between treatments should be read from left to right. The estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For the response rate and all-cause discontinuation, ORs greater than unity favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold.

Abbreviations: ARI = aripiprazole, BUP = bupropion, BUS = buspirone, CrI = credible interval, LAM = lamotrigine, LIT = lithium, MPD = methylphenidate, OLZ = olanzapine, OR = odds ratio, PBO = placebo, PDL = pindolol, QTP = quetiapine, RIS = risperidone, THY = thyroid hormone.

Main outcome: Only quetiapine (OR=1.92), aripiprazole (OR=1.85), thyroid hormone (OR=1.84) and lithium (OR=1.56) were shown to be superior to placebo based on response rates

Source: Zhou X et al. (2015): Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry 76(4):e487–98.

Figure 5: Lithium is singled out for prominence among augmentation strategies, although other augmentation methods may have yielded even better results than lithium in meta-analyses.

sant served as the appropriate comparative treatment[7] in the approval studies, with a switch of antidepressant at baseline in both the verum group (intranasal application of esketamine) and the placebo group (intranasal administra-

tion of placebo), and the choice of antidepressant was limited to SSRIs and dual antidepressants (SNRIs). In two other approval studies, a rapid effect within one day on depressive symptomatology as such was observed in patients with moderate or severe depression and concrete suicidal ideation although no statistically significant effect of intranasal esketamine (Spravato®) was observed on suicidality[8,9]. As a consequence, the following two indications were determined for intranasal esketamine (Spravato®), newly introduced to the market:

- Use in combination with an SSRI or SNRI in adults with treatment-resistant major depression who have failed to respond to at least two different antidepressant therapies in the current moderate-to-severe depressive episode.
- Use in combination with oral antidepressant therapy in adult patients with a moderate-to-severe episode of major depression as an acute short-term treatment for rapid reduction of depressive symptoms that are classified as being equivalent to a psychiatric emergency by a physician.

Examples of AMNOG application procedures in neurology for new drug approvals for multiple sclerosis include teriflunomide (no additional benefit resulting in a price reduction), ocrelizumab (additional benefit only for primary progressive MS, not for highly active relapsing-remitting MS), or sipolimod (secondary progressive MS, unlikely to receive additional benefit, but would be a desirable addition to the spectrum from the clinician's perspective).

References

[1] Deutsche Psychotherapeuten Vereinigung e.V. (2020): Report Psychotherapie 2020. Berlin.
https://go.sn.pub/pKBbu5

[2] https://go.sn.pub/xyPUpc

[3] https://go.sn.pub/aI2zMl

[4] https://go.sn.pub/CrKqTV

[5] Bschor T, Bauer M, Adli M (2014): Chronic and treatment resistant depression: diagnosis and stepwise therapy. Dtsch Arztebl Int 111: 766-776.
https://go.sn.pub/WFtbQB

[6] Zhou X et al. (2015): Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry 76(4):e487-98.
https://go.sn.pub/Izu3Ga

[7] Popova V et al. (2019): Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry 176:428-438.
https://go.sn.pub/dBdBRC

[8] Fu DJ et al. (2020): Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). J Clin Psychiatry 81(3):19m13191.
https://go.sn.pub/ToPjjc

[9] Ionescu D et al. (2021): Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). Int J Neuropsychopharm 24(1): 22-31.
https://go.sn.pub/2AHMet

Participation of medical societies in the AMNOG procedure – the example of oncology

Professor Thomas Seufferlein, President of the German Cancer Society, Clinic for Internal Medicine I, Ulm University Hospital | Dr Johannes Bruns, Secretary General of the German Cancer Society

Oncology is strongly represented in the AMNOG procedures in terms of case numbers. The Act for More Safety in the Supply of Pharmaceuticals (GSAV) stipulates that the scientific-medical societies must be involved in writing in all questions on the appropriate comparative treatment (ACT). Medical societies make extensive use of this possibility and contribute their expertise in 80 to 90 percent of the AMNOG procedures. In doing so, they also have to deal with the diverging perspectives of the IQWIG and EMA. Guidelines play an important role in determining the position of the medical societies. The definition of patient-relevant outcomes as well as their weighting or summation represent a further field of discussion. In addition, new fields of action arise from the option to request companies to conduct post-market data collection which is also specified in the GSAV. Medical societies in oncology are very active partners in the additional benefit assessment on many levels, i.e. in the hearing procedure, the preparation of guidelines, but also through participation in registries, certified centres, and tumour documentation. Over the years, quite a few processes in the AMNOG procedure have been improved.

Starting Point

The premises of the AMNOG procedure are clear: Among other things, an additional benefit of a new substance as compared to a comparator, the appropriate comparator treatment, must be demonstrated, patient-relevant endpoints must be validated to be eligible for a potential additional benefit, subgroup analyses must be mandatory and the additional benefit is determined by aggregating endpoints. Patient numbers must also be derived in a comprehensible manner, and post-market data collection is now also required (see figure 1).

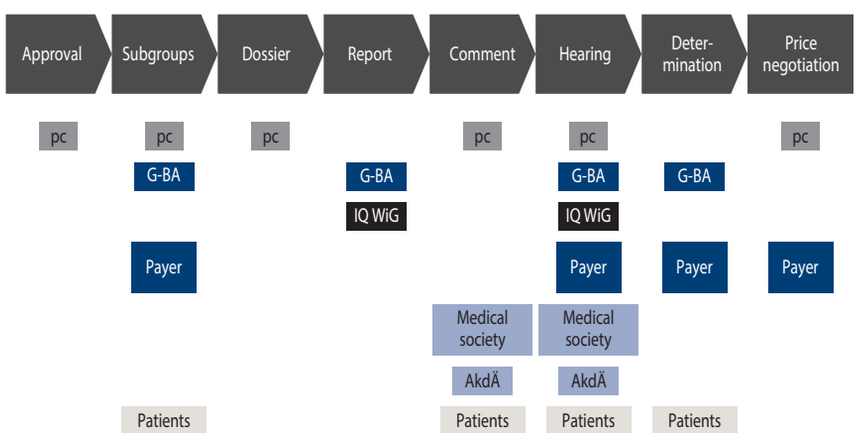
Due to a large number of therapeutic innovations in recent years, oncology has been strongly represented in AMNOG procedures. From 2011 to 2017, 139 of a total of 595 procedures in 18 specialties were attributable to oncology. With 235 of all procedures, oncology is the largest group in the AMNOG, followed by haematology with ten percent. Regarding the outcome of the procedures, a substantial additional benefit was most frequently awarded to oncology products[1] (see figure 2).

1. Participation of medical societies

The appropriate comparative treatment (ACT) plays an important role in the AMNOG procedure and is determined by the G-BA at the beginning of the procedure on the basis of its knowledge and research. Problems can arise, if no ACT has been defined or the selected ACT is no longer in line with state of science. The G-BA takes this circumstance into account by making it possible to change the ACT during the course of a procedure, if new findings are available that change the generally accepted state of medical knowledge. In order to determine the state of science, the involvement of the relevant medical societies has been requested for some time now.

Premises of the AMNOG procedure

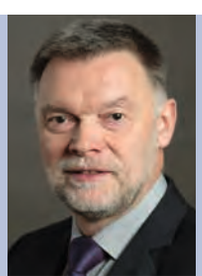
- **Appropriate comparative treatment**
  - Comparator determined by the G-BA against which the additional benefit must be demonstrated
- **Patient-relevant endpoints**
  - Mortality, morbidity and quality of life; surrogate parameters must be validated to be eligible for the additional benefit
- **Subgroups**
  - Subgroup analyses must be presented
- **Determination additional benefit**
  - Through aggregation of endpoints
- **Patient numbers**
  - Comprehensible derivation of patient numbers required
- **Post-market data collection**



Source: AWMF/DGHO 2019

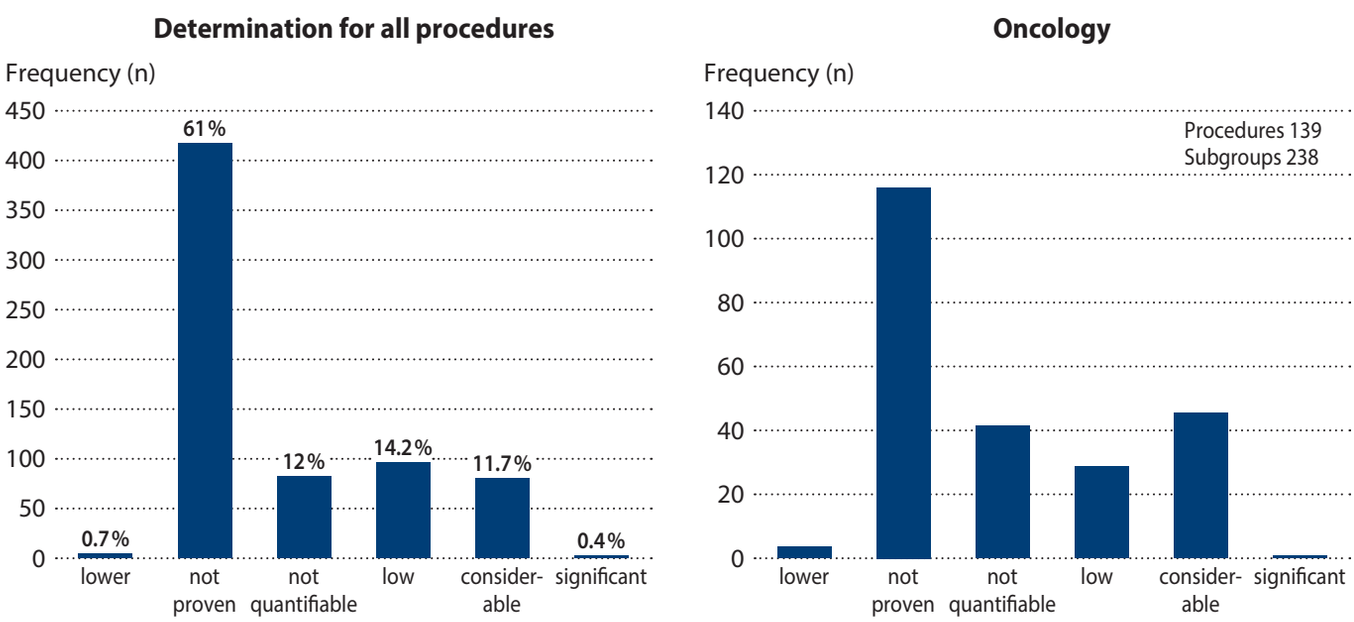
Figure 1: Due to the tight time frame of the AMNOG process, a statement must be submitted within a few weeks.

Professor Thomas Seufferlein *is President of the German Cancer Society. He studied medicine in Regensburg and Munich. After several years of research in Great Britain, he moved to Ulm in 1996. He worked there until September 2008, among other things as senior consultant. After his subsequent four-year stopover in Halle (Saale) he returned to Ulm University Hospital as Medical Director of the Clinic for Internal Medicine I.*



Dr Johannes Bruns *has been Secretary General of the German Cancer Society, Berlin, since 2006. He studied medicine, mathematics and sports science at the University of Bonn and, after working as a physician at the Clinic and Polyclinic for Trauma Surgery, he first worked as a research assistant in the German Bundestag. He then worked as head of the department for Fundamental Issues of Medical Care at the former VdAK.*

Evaluation of the additional benefit in all procedures and in oncology 2011–2018



Quelle: AWMF/DGHO 2019

Figure 2: With 139 of 595 procedures, oncology is the most represented specialty in the early benefit assessment, ahead of haematology. In more cases than average, a „considerable" additional benefit was awarded.

This demand was addressed with the Act for Greater Safety in the Supply of Medicines (GSAV) stipulating that the scientific-medical societies must be involved in writing in all matters relating to the ACT. The medical societies make active use of this possibility and actively contribute their expertise in 80 to 90 percent of the AMNOG procedures (see figure 3). In addition to a high level of expertise of the medical societies, this also requires a fast responsiveness and a professional team to answer questions. This places high demands on the medical societies, especially if a large number of requests comes in, since there is no consideration for the evaluation carried out, i.e. the work is done on a voluntary basis and a significant infrastructure must be maintained.

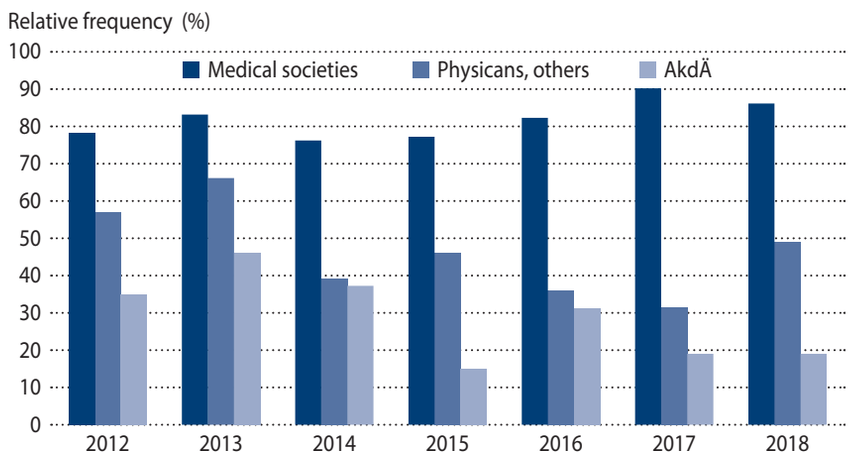
Of course, the medical societies also have to deal with the different perspectives the IQWIG and EMA have. While the IQWIG methodologically focuses on diagnosis, subgroups, quality of life, survival and costs in its HTAs, indication, pharmaceutical quality, efficacy and safety as well as the benefit-risk ratio are of primary importance for regulatory authorities such as the EMA. For medical societies, the benefit of a pharmaceutical for patients is paramount. In this context, the extent to which the state of medical knowledge presented in a clinical study can be realised in

Participation of scientific medical societies

- Involvement only after publication of the IQWIG's or G-BA's report, respectively, as parties entitled to submit comments
- Proportion of participation of scientific-medical societies **approx. 80 to 90%**
- Very active partner in the additional benefit assessment

Prerequisite:

- High level of expertise
- Fast responsiveness
- Professional team
- High requirements for MSs (without return)
  - DGHO, AWMF with excellent performance



Source: AWMF/DGHO 2019

Figure 3: Over the years, medical societies have contributed their expertise in 80 to 90 percent of AMNOG procedures.

everyday clinical practice should also be considered. This clinical benefit assessment is based upon the patient's own experience as well as registry and guideline data, and the assessment itself is incorporated into the guidelines as a recommendation (see figure 4).

Role of guidelines

Guidelines initiated and supported by medical societies are well established in oncology and are essential for the quality-assured care of oncology patients. The Oncology Guidelines Program (OL) of the German Cancer Aid, German Cancer Society and AWMF currently covers more than 90 percent of the major tumour entities. Many of the guidelines are already structured as so-called „living guidelines" with regular updates during the year. In addition, new data from science into guidelines can quickly be implemented by means of amendments. Thus, the guidelines can increasingly meet the requirement for timeliness. A prerequisite for these processes was the introduction of a content management system for the OL. As a next step, a

Different perspectives in the approval and the HTA procedure

EMA/approval assessment	HTA/additional benefit
■ Indication/Off label use	■ Diagnosis
■ Pharmaceutical quality	■ Subgroup
■ Efficacy	■ Quality of life
■ Safety	■ Survival
■ Benefit-risk ratio	■ Costs

Quelle: Own representation

Figure 4: IQWiG focuses on different points in its reports than the EMA does during the approval procedure.

position is currently being established in the OL for data analysis from HTAs from IQWIG, FDA, EMA, and other organisations. These reports must be processed and continuously made available to the guideline groups for the update of guidelines.

Endpoints of studies in the AMNOG procedure

A major point of discussion for the medical societies in the AMNOG procedure is the question of the appropriate endpoint of a study. Here, too, there is a discrepancy between the criteria of the regulatory authorities and the additional benefit assessment. Regulatory authorities accept significantly more morbidity endpoints than are accepted for the benefit assessment of a pharmaceutical. These include survival rates at a certain point in time or disease-free and event-free survival, which can be relevant endpoints from a clinical point of view, especially in therapy-naïve patients, as they capture therapy failure and therapy-associated lethality and are less influenced by comorbidity, but also post-progression therapies. These endpoints are viewed critically in the AMNOG process and are hardly recognised.

The weighting of patient-relevant outcomes is also a point of discussion: How do you weight e.g. a prolongation of survival, improvement of quality of life, and reduction of side effects? Patient-specific factors play an important role here, e.g. any previous therapy, specific comorbidities, but also specific patients' expectations. Medical societies can give important impulses from their clinical experience that are difficult to capture in a purely methodologically oriented approach.

From the medical societies' point of view, it is problematic to just summarise the partly diverging side effects within the scope of early benefit assessment even without differentiation of the clinical severity. In general, the question arises as to what extent side effects can simply be added up, since they affect patients in very different ways. Thus, although a summation of side effects against clinical endpoints is possible, it is only useful to a limited extent. After detailed information has been provided about both benefits and side effects, the patient's decision is essential which also includes the individual assessment of the clinical impression of the attending physician. It must also be taken into account that data on side effects is often not yet available in the early benefit assessment, e.g. because certain patient groups – such as elderly patients – are underrepresented in clinical studies and the management of side effects is not yet optimally established, especially in case of very innovative substances. This demonstrates new fields of action for post-market data collection.

Post-market data collection in oncology

The Act for Greater Safety in the Supply of Medicines (GSAV) authorises the G-BA to request post-market data collection, case-control studies or registry studies from the pharmaceutical company for new pharmaceuticals. This is intended to generate further evidence after approval on pharmaceuticals for which the evidence base was insufficient at the time of the benefit assessment, e.g. for pharmaceuticals with accelerated approval or orphan drugs. In principle, this is the right step. The IQWIG has elaborated scientific concepts for the generation of treatment-related data and their analysis for the purpose of the additional benefit assessment. In this paper, the IQWIG states, among other things, that treatment-related data collected for the purpose of the additional benefit assessment of pharmaceuticals must be sufficiently valid and structured.

However, since the collection of treatment-related data is carried out without specific specifications, certain data that are required for the additional benefit assessment are not documented for all patients in daily clinical practice.

This includes, for example, health-related quality of life or the comprehensive documentation of side effects. Specific registries and electronic patient files which could be accessed for post-market data collection either not available or these do not comprise all areas or entities or are not sufficiently accessible for data protection reasons. In many cases, accounting data of health insurances are often not helpful, since e.g. patient-reported outcomes are not included.

The IQWIG states that even if healthcare data is used, a study-based comparison between the new pharmaceutical and the appropriate comparative treatment as defined by the G-BA is required. However, in practice, this is almost never the case. Thus, the IQWIG's request for at least comparative studies without randomisation with the necessary endpoints on mortality, morbidity, quality of life, and side effects is difficult to realise, even if the IQWIG concedes that comparisons with historical controls are also an option.

The methodological requirements for post-market data collection must be integrable into the daily clinical practice, available endpoints must be specified and confounders as well as further requirements must be transparent in advance. A list of existing, usable data sources or registries is desirable, including quality criteria and meta-data that largely meet most of the G-BA requirements. Thus, there is an urgent need to strengthen and further develop already existing registry structures in oncology, especially regarding the specific analysability of treatment data, e.g. in the context of post-market data collection.

In its position paper on „Knowledge-generating oncological care" of 2017, the DKG stated[2]: „To achieve reliable evidence after approval of new pharmaceuticals, post-approval studies are the gold standard. In addition, new additional forms of evidence generation (healthcare studies, cancer registries) must be reflected. Funding for these measures must be ensured. These measures are controlled by a national institution that must be knowledge-(science)-driven." In its first stage, the new federal Cancer Registry Data Act provides for the pooling of cancer registry data by the Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute.

Conclusion

Medical societies in oncology are very active partners in the additional benefit assessment, and this on many levels, i.e. in the hearing procedure, preparation of guidelines, but also through their involvement in registries, certified centres and tumour documentation (see figure 5). Over the years, a number of AMNOG processes have been improved, but the evaluation of endpoints for the additional benefit assessment by methodologists and medical societies still diverges.

Post-market data collection is a first, meaningful step to generate further evidence on pharmaceuticals after approval, but it is also a challenge. The criteria that have been established by IQWIG are demanding and are currently only partly fulfilled, even by cancer registry data. However, since the registries already exist and the pooling of registry data is subject to statutory regulation, this should be an incentive to promote the development of registries as well as the evaluation of the data collected for healthcare research. Ultimately, all these measures must serve the patient, and a maximum benefit can only be achieved through the cooperation of all stakeholders.

Conclusion: Participation on the example of oncology

- Oncology is an active partner in the benefit assessment
  - at many levels, e.g. medical societies, guideline groups, registries, ADTs, etc.
- Several points in the procedure have been improved (ACT)
- Discrepancy between approval procedure and benefit assessment with regard to endpoint assessment still difficult (objective)
- Post-marketing data collection important, but also challenging:
  - Criteria demanding
  - Cancer registry data partly suitable
    - Further develop registries (ZFKD and more)
    - More support for public registries and centres for more comprehensive data collection (example UK)

Quelle: Own representation

Figure 5: Post-market data collection is a first, meaningful step to generate further evidence on pharmaceuticals after approval, but it is also a challenge.

References

[1] Positionspapier von AWMF und DGHO: Frühe Nutzenbewertung neuer Arzneimittel in Deutschland 2011-2018 - Gerechtigkeit und Nachhaltigkeit; Band 13 der Gesundheitspolitischen Schriftenreihe der DGHO. https://go.sn.pub/75dw7n

[2] AG Zukunft der Onkologie; Positionspapier zur „Wissen generierenden onkologische Versorgung" Deutsche Krebsgesellschaft 2017 https://go.sn.pub/o18Tfb

The role of medical societies within AMNOG from the political perspective

Professor Andrew John Ullmann | Member of the German Bundestag

In order to understand the role of medical societies in AMNOG, it is necessary to understand the basic principles of the AMNOG procedure. With the Pharmaceutical Market Reorganisation Act (AMNOG) of January 2011, the prices of innovative pharmaceuticals in Germany were regulated. Prices for patent-protected pharmaceuticals are determined on the basis of an additional benefit assessment. Health insurance providers then pay the price that reflects the additional benefit of the respective pharmaceutical. Thus, prices are kept within an affordable range without hindering innovations in the market that ultimately improve the treatment of patients in the long term.

The decision on the additional benefit of a pharmaceutical is made by the Federal Joint Committee (G-BA). This highest body of self-government in Germany consists of representatives of payers/health insurance providers and service providers. From the service providers, the German Hospital Federation, the National Association of Statutory Health Insurance Physicians (KBV), and the National Association of Statutory Health Insurance Dentists share the seats on the G-BA. In addition, there are three impartial members. The additional benefit assessment by this panel provides the basis for price negotiations in the statutory health insurance system. The entire process normally takes twelve months. The reimbursement rates take effect immediately and apply to both statutory and private health insurances.

Due to the significance of the AMNOG procedure for the German healthcare, the best information must be available during the procedure. Moreover, general practitioners who treat patients and later use the new pharmaceuticals must be broadly involved in the evaluation process. Merely seating on the G-BA only as a voting representative does not do justice to the broadly available medical know-how. Medical societies must participate even more in the consultations about the appropriate comparative treatment.

I also share the assessment of the Association of the Scientific Medical Societies in Germany (AWMF) and the German Society for Haematology and Medical Oncology (DGHO) that the early benefit assessment must remain transparent and can be carried out in a timely manner without a large number of additional reports. Moreover, physicians must be fully informed about the results of the benefit assessment and within the context of the guidelines, and the pricing procedure must be legally binding. I also share the view that follow-on benefit assessments are necessary to achieve sustainable determinations, and that these should also take health economic aspects into account.

The role of the medical societies in the AMNOG was most recently strengthened in the Act for Greater Safety in the Supply of Medicines (GSAV). Paragraph 7 in Section 35a SGB V was adapted for this purpose. The previous version read: „(7) The Federal Joint Committee shall advise the pharmaceutical company in particular on documents and studies to be submitted and on the comparative treatment. It may reach agreements on this with the pharmaceutical company. Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (PEI) should be involved in the consultations before the start of phase-II studies or for the planning of clinical studies. The pharmaceutical company receives a transcript of the consultation. Further details, including reimbursement of the costs incurred for this consultation, shall be regulated in the Rules of Procedure."

In this paragraph, the following sentence was added: „Regarding questions of the comparative treatment, the scientific-medical societies and the Drug Commission of the German Medical Association (AKdÄ) shall be involved

in writing in due consideration of business and business secrets of the respective pharmaceutical company."

This new provision in the GSAV is well received, because most scientific-medical societies have a wide experience both in the preparation of guidelines and in medical practice. Until now, the involvement of the scientific medical societies was only possible within the framework of the hearing procedure. An early involvement in the determination of the appropriate comparative treatment is therefore important.

In the future orientation of the benefit assessment procedure, the medical-scientific societies must continue to play a key role, because they are more familiar with the challenges of clinical-medical practice. In what form this will take place, however, requires further debate.

Professor Andrew John Ullmann
is a member of the FDP and has been a member of the German Bundestag since 2017. He is Professor of Infectiology at the Julius Maximilians University of Würzburg and a specialist in internal medicine, haematology, internal oncology and infectiology.

Patient representatives in the G-BA – is there really a need for reform?

Dr Jürgen Bausch | Paediatrician and Honorary Chairman of KV Hessen

Involvement of those affected in the decisions of institutions whose work can have a direct impact on each individual is a fundamental democratic principle. We know from experience that such rights of participation can sometimes facilitate required processes, but might also hinder them, e.g. in case of an expansion of highways or new wind turbines and railway lines, but also in the demand planning of hospitals or outpatient care by statutory healthcare.

Decisions on the use and reimbursement of pharmaceuticals covered by the statutory health insurance affect individual patient interests. This includes some wishful thinking that is not necessarily evidence-based (e.g. alternative medicine as a health insurance benefit). About 20 years ago, this problem was first addressed on a broader scale in outpatient pharmaceutical care.

Based on a legal requirement, i.e. the Positive List for Drugs Act (AMPoLG), the Ministry of Health appointed a Positive List Commission consisting of nine members to evaluate all pharmaceuticals on the German market to create a list that should become the basis for prescriptions in outpatient care by SHI-accredited physicians. The task for the commission as stipulated by the law was: All pharmaceuticals that can prove a „more than minor benefit" for SHI patients are to be positively listed.

Ample resistance to the positive list

There was plenty of criticism and resistance when this positive list – that had been desired by the majority of SHI physicians at the time – was completed in the second attempt. Initially, this came from negatively affected manufacturers and their powerful pharmaceutical associations, but also from patient organisations, i.e. as previously reimbursed and common pharmaceuticals had not been positively listed, because – from the Commission's point of view – they did not demonstrate „more than a low benefit". Despite the fact that it had successfully overcome all approval hurdles of the European Medicines Agency (EMA) or the Federal Institute for Drugs and Medical Devices (BfArM). For the first time, the term „benefit" of pharmaceuticals appeared in the SGB V alongside the far more familiar term of regulatory approval.

For higher political reasons, the positive list disappeared in the drawers of the Federal Ministry of Health and never became effective. But it had become apparent during the consultation process that the evidence of benefit for many common but also for some new active ingredients that are very popular among prescribers and patients, was so poor that health policy makers from both the government and the opposition discovered this lack of expert evidence on the benefit of pharmaceuticals as an area of political action.

A new beginning with the establishment of IQWiG

This cross-party realisation resulted in a rather quiet and unspectacular agreement between major health policy makers in the government and the opposition in autumn 2003: The positive list was discarded and a new start made in mid-2004 with the establishment of the influential Institute for Quality and Efficiency in Health Care (IQWIG) to enable the Federal Joint Committee (G-BA), among others, to provide prescribing physicians and payers with tested evidence-based findings.

The aim is to make SHI prescriptions that are covered by the statutory health insurance more rational and efficient. Pharmaceuticals with controversial effects or insufficient evidence of benefit should no longer be prescribed at the expense of the health insurances.

Instead of creating ever new „prescription lists", the G-BA, also with the help of IQWIG, quickly switched to bin-

ding treatment data for statutory health insurance physicians as part of the pharmaceutical guideline. And beginning of 2004, patient representatives were included in the G-BA's consultations for the first time. In the initial phase, these representatives came directly from the relevant disease-related patient self-help organisations as experts in their own diseases. Until today, these patient representatives in the G-BA have the right to speak and make applications, access all available information. However, they have no voting rights if the representatives of the health insurances and physicians do not agree on the benefit of the pharmaceutical for patients despite approval and a majority decision became necessary.

To date, this basic structure has not changed – despite various changes, e.g. granting access to the committees of the G-BA (e.g. inclusion of the hospital association on the physicians' side or legal ordinance on the legitimacy of patient representatives in the G-BA). Not to mention the Pharmaceutical Market Reorganisation Act (AMNOG) that came into force ten years ago with its early benefit assessment. Of course, this was done with the involvement of patient representatives, who now have their own staff office at the G-BA.

Thus, patients participate in G-BA decisions, although their means do not seem to be equivalent. No wonder that time and again the demand arises – for very different motives – that patient representatives should also be given a formal right to vote, which until now has only been available to the representatives of the health insurances and physicians in the practised self-government in parity.

However, this fundamental democratic approach would have considerable and unforeseeable consequences in the construct of self-administration. For this reason, whenever this question comes up again – as is the case quite regularly, especially in parliamentary elections – all knowledgeable experts wave it off.

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Is there more than a formal need for change?

The question after some sixteen years of participation of patient representatives in the G-BA is: Is there a need for change in terms of content and not just a formal need for a new decision-making practice by the G-BA, because patient interests are grossly disregarded?

Or, in other words: Is the current participation of patients in the G-BA only a democratic fig leaf? The majority of those authorised to represent patients does not claim this. And the impartial chairman of the G-BA, Professor Josef Hecken, emphasises the active participation of patient representatives in the decisions of the G-BA again and again. Especially when it comes to the early benefit assessment of pharmaceuticals. This does not exclude controversial assessments in individual cases. These take place time and

again between physicians' and health insurers' representatives.

Even in the age of evidence-based medicine, stakeholders arrive at different opinions, even if the available data is equal. And that is why an impartial chairman with his two impartial deputies is indispensable in the self-administration of health insurances and Regional Association of SHI-Accredited Physicians.

Patient representatives and medical societies: essential resources in the AMNOG

Dr Florian Staeck

An appropriate involvement of patient concerns and findings of scientific medical societies in the process of early benefit assessment is not only associated with the hope of an appreciative consideration of the aspects contributed by patients and experts. This approach is also associated with the expectation that greater participation of these stakeholders will influence the grading of an additional benefit, where necessary, thus ensuring a more patient-centred care in the long term.

Participants of the 13th meeting of the Interdisciplinary Platform on Benefit Assessment agreed on this point. Due to the pandemic, the conference, titled „Patient organisations and medical societies: what is their role in benefit assessment?" was held online on 19-20 March 2021.

Beyond this general consensus, a broad spectrum of opinions emerged among participants on whether and, if so, through which steps this can succeed. One group spoke out in favour of participation formats that go beyond the current consultation rights in the AMNOG procedure. However, another group of participants questioned the actual relevance of supposed deficits in the current governance structure. Among other things, they referred to the procedure with a very tight schedule that ultimately has only a preparatory character for the subsequent price negotiations. In view of the tight deadlines, those who favour a stronger participation into the procedure of the Joint Federal Committee (G-BA) would quickly reach limits, they warned. Other participants argued that recruiting „professional" patient representatives could be at the expense of individual patient interests and even interfere with the intention of a stronger care orientation.

Other participants replied that participation of trained patient representatives in the AMNOG procedure represented an indispensable resource, as patients could contribute their specific knowledge based on their own experience, especially after a serious disease. For the patients' perspective provided insights into the practical problems of routine clinical practice. Patients and their attending physicians often came to divergent assessments in the course of treatment with regard to risks, side effects, or quality-of-life aspects of therapeutic interventions. In a survey, hair loss and neuropathies, for example, had been rated quite differently by myeloma patients and their attending physicians. The same applied to risk-benefit assessments of diagnostic procedures, they said.

Important notarial function of patient representatives

Of course, the characteristics of the respective disease determine the possibility of effective patient representation by those affected: In case of dementia or paediatric diseases, this usually has to be done by the relatives. In contrast, HIV/AIDS patients are often very well informed about their disease and have excellent networks. At the same time, the necessary independence of patient representatives can interfere with the need to provide infrastructure and expertise.

Participants argued that patient representatives already had an important notarial function in the early benefit assessment procedure: they emphasised that they were witnesses to the fact that all decisions are based on sufficient evidence; this strengthened the credibility of the procedure. However, concrete system failures based on examples – with regard to the current early benefit assessment process – would not be addressed.

The following points were discussed regarding to the pros and cons of a stronger involvement of patient organisations:

- **Steps taken so far to strengthen the role of patient representatives:** Participants pointed out that the G-BA as the coordination body and sub-legislative standard-setting

body was without parallel. Thus, the integration of patient representatives into the consultation process, which was initiated in 2004, also took place without an existing role model. Since then, an ongoing empowerment process had taken place, so that in the meantime every larger patient organisation had a representative with the necessary competence to represent patient interests in the AMNOG process, they explained. Therefore, a lot had happened since then to change the patients' role from being affected to being involved as stipulated in the Patient Rights Act of 2013.

This was also shown in the National Decade against Cancer where patient participation was first specified as one of seven priority goals. Another „footprint" of the work of patient organisations could be seen in the increasing consideration of quality of life as an endpoint in clinical studies. They argued that this was an important corrective to ensure that side effects of a therapy are sufficiently considered in the evaluation process.

Another task for patient organisations arose from the requirements for a quality-assured use of a pharmaceutical by the G-BA. Here, they said, care would have to be taken in the consultation process that the actual care processes were sufficiently taken into account in the sense of „patient pathways".

In view of this multitude of tasks and in view of 90 procedures of the early benefit assessment in 2020, patient representation needed to be further professionalised. However, the effort to find qualified personnel was constantly increasing. In view of the often all-day meetings in the subcommittees of the G-BA, there was an increasing risk of staff overload. Even the staff unit set up in the Federal Committee could only compensate this to a limited extent. Patient representation as an honorary office would gradually reach its limits, and further structural strengthening was necessary, they demanded.

Moreover, new challenges for patient participation arose from the changing structure of self-help, it was reported. The proportion of patients who are permanently involved tended to decline in recent years, and younger patients often only participate on a project basis. This would make it even more difficult to recruit qualified representatives.

- **On the question of the democratic legitimacy of patient representatives:** The legitimacy of the input of the groups in the G-BA varies. Whereas the legitimacy of the service providers' bench could be derived from the „electorate" of physicians in private practice, the legitimacy of the health insurance fund representatives was rather weak due to the often criticised social elections, participants explained. The situation for patient representatives was similar: Here the Federal Ministry of Health had nominated four relevant associations on the basis of the Patient Participation Ordinance, whose work is coordinated by the BAG self-help. However, this legal construction had not yet been objected to by the Federal Social Court, since the weak input legitimation was accompanied with a very narrow set of standards in the Social Code V, they outlined. This was also complemented by the legal supervision of the Federal Ministry of Health.

Other participants replied that the democratic legitimacy of patient representatives was not that weak. For the Patient Participation Ordinance, they referred to the basis for authorisation in Section 140g of the German Social Code, Book V, which created a continuous chain of legitimation for patient representatives. And on the other hand, the coordination committee expressly mentioned in Section 140f (8) SGB V – which had thus been anchored as an institution in the healthcare system.

Nevertheless, the current legitimacy of patient organisations was described as „thin" in the debate in order to pro-

claim a right to vote or veto votes in the G-BA based on this. According to the thesis, there was currently no basis in the law for such a step. Instead, a new Patient Participation Ordinance was proposed as a thought alternative, specifying competencies that applying patient representatives have to have. The BMG could then – based on the required competencies – create a list of all patient representative candidates. Finally, it would be up to the German Bundestag to elect suitable candidates from this list. They proposed that, in this way, a legitimation for more extensive participation rights of patient representatives could be established.

- **Options for stronger structural involvement of patient representatives in the early benefit assessment procedure:** A rather cautious position towards a formal legal strengthening of patient representatives was justified in the discussion with the fact that so far – so the assertion – it was never apparent that decisions in the G-BA had been made against their will. This was opposed with the argument that this purely output-oriented view didn't go into sufficient deep: According to the opposing thesis, patient representatives were not yet in a position making it necessary to overrule them.

Other participants in the discussion described the current influence as a construction that is de facto located between the right to be heard and the right to co-decide. For example, patient representatives would have the right to speak as well as the right to be present when the decision is taken. On the other hand, they could not demand that the plenum of the G-BA justifies divergent decisions that contradict the position of the patient representatives. Other participants described the position of the patient representatives – particularly in Section 35a Committee – as strong, since the Committee attempted to reach consensual decisions. Due to the negotiation processes in the run-up to the plenary decision in the G-BA, the right of co-counselling de facto comes close to a voting right, so that a formal voting right of the patient bench was dispensable.

Moreover, it was advocated that the question of voting rights should always be discussed in relation to the individual committees in the G-BA. Thus, it was considered that an additional bench of patient representatives with voting rights could very well promote patient orientation in committees for method evaluation or quality assurance. In other constellations, e.g. the benefits catalogue for dental prostheses, a voting right of patient representatives, would not present an added value, if neither the representatives of the health insurances nor the representatives of dentists had an interest in expanding the corresponding benefits, it was argued.

- **Patient representation at European level:** Participants controversially debated the extent to which the process of patient participation had been implemented more consistently in other countries. The United Kingdom was cited as an example. There, the involvement of patients – and of citizens, such as in the Citizen Council – had a longer tradition than in Germany. Other participants replied that the benefit assessment process in the German AMNOG system was characterised by consistent transparency. In Germany, there wasn't such a thing like blacked-out passages, as in NICE dossiers. Against this background, UK's role model function was called into question at this point.

It was pointed out that in Europe patient participation had already been „part of everyday life" for ten years. Patient representatives were firmly integrated into various programmes, such as Horizon 2020 at EU level and were also active partners of medical societies. The same applied to the participation in the committees of the European Medicines Agency (EMA). Participants also mentioned the EU Regulation 536/2014 on clinical studies of medicinal pro-

ducts for human use, requiring specification in the protocol where patient representatives are to be involved.

Germany, on the other hand, had a strong and well-established self-help structure, but lagged behind other EU countries in the systematic involvement of patient representatives in clinical research, it was reported. Especially here, their early involvement would be necessary, when decisions about the design of clinical studies are taken. This was precisely where the influence of the patient's perspective could be strongest: It was a matter of asking the „right" questions in the research process, for example with regard to the criteria to be chosen to measure the patient's quality of life in studies. But so far, representatives from German patient organisations had been under-represented in these committees.

Similar to the debate on the status quo and the need for reform in the involvement of patient representatives in the AMNOG procedure, the participants of the platform meeting discussed the involvement of medical societies in the procedure of early benefit assessment. The discussion focused on the following aspects:

- **Status quo of the integration of and challenges for medical societies:** In 2015, a standing committee on „Benefit assessment of pharmaceuticals" was set up at the AWMF to bring together the expertise of 179 medical societies from all areas of medicine. This proved to be highly successful, as medical societies are involved in around 85 percent of G-BA procedures for early benefit assessment, it was reported. In oncology, this rate was even as high as 97 percent, because in view of the high number of new oncology products, the relevant medical societies are particularly often involved. In haematology and dermatology, as well as in infectious diseases, participation was also above average. Participants reported that, in contrast, the rate was below average in diabetology, for example, in cases where the G-BA frequently did not determine an additional benefit.

Overall, the rate of participation of medical societies in AMNOG procedures had increased in recent years. This was also associated with an increased workload for the requested experts, so that it requires a special motivation to get involved in the case of a request by the AWMF Commission, they outlined.

Until 2019, medical societies had been involved exclusively within the framework of the hearing, i.e. in a rather late phase of the AMNOG procedure. They noted that there were different positive perceptions of these hearing procedures in the individual specialties. The resource problem had again intensified since the new regulation by the Act for Greater Safety in the Supply of Medicines (GSAV) was adopted in August 2019. Thus, individual medical societies were repeatedly forced to decline requests for comments during the hearing procedure. This applied particularly to experts who are already occupied over several years, for example, with the development of an S3 guideline.

In the vast majority of cases, the assessment of the dossier submitted by the pharmaceutical company was not the most urgent issue from the perspective of the medical societies, but rather the classification of a new substance in the treatment standard with regard to guidelines and aspects of care. Moreover, medical societies were highly interested in involving patients who, for example, have already gained experience with the new pharmaceutical in clinical studies.

In the overwhelming majority of cases, medical societies reached a consensus when submitting their statements. However, there had also been cases of dissent within the AWFM commission, which might be due to different therapeutic strategies in different treatment settings, it was reported.

Overall, participation of medical societies in the AMNOG procedure was described as a reciprocal process: Experts contribute their expertise, and in return they receive information from the dossiers through the transparent procedure that had not yet been published elsewhere at the time. The statement procedure also almost automatically increased communication with colleagues from other medical societies. The reason for this was because the evaluation grids regarding the determination of the ACT often vary, so that the comparison of different positions took place in the course of the development of a joint statement.

- **New challenges for medical societies, especially in the context of the GSAV:** The GSAV created a new challenge for medical societies - since then, they can already be involved in the determination of the appropriate comparative treatment (ACT). Participants outlined that in this procedure the participating medical societies made one common statement. Thus, the scientific consensus building took place before the submission of the statement on the ACT. From March to December 2020 alone, there had been 224 inquiries from the G-BA, and in 191 cases (85 percent) a corresponding comment had been made. They explained that the extended deadline was important in the context of the new regulation, i.e. statements had to be submitted within five weeks instead of three weeks.

A more recent development was that medical societies were increasingly being requested by the G-BA to consider endpoints in studies, although this had not yet been legally implemented. In this context, the high number of requests was a further stress test for the voluntary commitment of all stakeholders. In the discussion, therefore, there were isolated calls to extend the time schedule of the procedure. Participants proposed an additional explanation period in case of dissent between medical societies. Other participants replied that the inclusion of ever more consultation sessions within the existing AMNOG deadlines would very quickly reach system-immanent limits.

They also noted: Formal deadlines alone were not decisive for the question of when a new pharmaceutical actually reaches the healthcare system – especially since every new active ingredient was available in Germany from the time of approval. In many cases, the decisive factor was the traditional reluctance of many prescribing physicians in Germany to wait until the therapeutic value of a new pharmaceutical had been established in the healthcare system.

In the discussion, agreement on an ACT was described as a particular challenge, if no ACT has been specified in the relevant guidelines or the guideline is obsolete. This applied similarly to the weighting of patient-relevant outcomes. This was due to the fact that the internal relationship of elements, such as improvement of the quality of life or reduction of side effects is highly patient-individual – and the subjective perceptions of patients of side effects often diverge widely. Methodologically, the question of which parameters should be measured at what appropriate times was particularly challenging. Here, post-market data collection in accordance with Section 35a, Paragraph 3b of the German Social Code, Book V would open up new perspectives. Participants requested that, for this purpose, existing registers would have to be further developed in terms of analysability. The common objective would have to be knowledge-generating care, in which the additional benefit assessment can advance the treatment process that is reflected in guidelines.

- **Options for a better support and structure formation at medical societies:** Driven by the desire to involve medical societies even more in the early benefit assessment procedure, there were only isolated calls that medical societies should get their own bench with voting rights in the G-BA. This was mostly met with scepticism. It was

undisputed that it makes sense to involve medical societies at an earlier stage in the procedure – as was recently done with the GSAV. It was argued that if the healthcare perspective was taken into account at an early stage, this could help to avoid subsequent consultation sessions.

However, the priority should be to ensure that in the AMNOG procedure expertise gets to where it is needed. Against this background, the current approach of involving medical societies only via a hearing procedure was not sufficient. Alternatively, they could be involved in the technical work of the subcommittees of the G-BA, it was suggested. Since medical societies and the quality of the benefit assessment process mutually benefit from this process, increasing the „contact areas" of the exchange seemed feasible. Participants emphasised that no legal requirement was necessary for this, since the members of the subcommittees and the management of the G-BA could consult external expertise at any time.

In view of the limited human resources in the medical societies, participants called for more structural support, not primarily for the support of individual experts. This infrastructural support of medical societies was partly already practised today, but should be expanded, it was argued. In particular, the aim was to show appreciation for the experts involved. Infrastructure funding could also enhance medical societies' responsiveness – in times of an increasingly intense exchange between the G-BA, patient organisations, medical societies and other stakeholders.

However the involvement of patient organisations and medical societies in the AMNOG procedure would be regulated or reformed in future: The majority of participants of the platform meeting were convinced that this process would have to be dynamic opening up mutual learning steps in the sense of more patient-centred care.

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Patients and medical societies: Additional expertise for AMNOG

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