

## Gene therapy ante portas

### – Appropriate solutions for the reimbursement dilemma



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*Gene therapies are widely regarded as promising but not yet fully developed therapeutic strategies for the treatment of very rare and otherwise non-treatable diseases. The high expectations were dashed in the early phases of research and development in the 1970s and not even the decoding of the human genome at the end of the nineties could inaugurate the beginning of a new age of gene therapies. After the first gene therapy, Glybera<sup>®</sup>, was approved in Europe, it was withdrawn from the European market due to disappointing results, letting many protagonists of the health care system consider the gene therapeutic approach to be questionable and having limited potential. However, current and very impressive study data suggests that several highly potential gene therapies will access the German market in the upcoming years. Since the paradigm of gene therapy follows a completely different logic than conventional therapies and because gene therapy costs a multiple of common innovative pharmaceuticals, payers are going to face a considerable challenge that cannot be handled with traditional instruments. Here, the authors explain challenges regarding the reimbursement of gene therapies and discuss possible solutions for the health insurance system.*

**O**n August the 8<sup>th</sup>, 2017, the press agency Reuters reported: ‘*The science of gene therapy is finally delivering on its potential, and drugmakers are now hoping to produce commercially viable medicines after tiny sales for the first two such treatments in Europe*’. So far, neither the clinical data nor the business model of gene therapy were convincing, resulting in the overall impression of gene therapy as being an experimental approach only, that won’t establish itself enough to play a role in standard care for quite some years. However, the clinical data sets from advanced clinical trials, the immense investments in therapeutic concepts and production sites by the major pharmaceutical companies, the evaluation of gene therapy companies by the financial

community as well as the well-filled pipelines of these companies, rather indicate the beginning of gene therapy approaches, which will re-define our therapeutic standards in various fields. This leads to a shift in the paradigm of the curative approach and the associated cost logic: away from a chronic, most often lifelong treatment with calculable and broadly constant overheads to an extremely high one-time expenditure, which might lead to a life-long healing without further costs. The existing health insurance algorithms, both in private as well as in statutory health insurance, are not applicable to this completely different logic of value creation. Therefore, new actuarial approaches have to be developed and embedded in the supply contracts. What exactly makes gene therapy so special?

## Mechanisms of action of gene therapy

Gene therapy generally involves the insertion of genetic material (such as DNA or RNA) into cells of the body. Gene therapy aims to correct an inherited or acquired defect within the genome of the cell and thus to completely restore the production of a missing protein or to normalize the expression of a certain gene. In somatic gene therapy only differentiated cells and their precursors are targeted, leaving gametes and germ cells unaffected, thus preventing the therapeutic modification to be passed on to potential offspring. Somatic gene therapy aligns with the German Embryo Protection Act, which states that therapeutic effects must be limited to the individual patient only and not passed on to potential offspring. Gene therapy not only allows symptomatic treatment of certain diseases but a treatment on the molecular level. A gene therapeutic approach is defined as a biological drug used *in vivo* or *ex vivo*, which consists of or involves nucleic acids for regulation, repair, replacement, addition or removal of genes and whose therapeutic, prophylactic or diagnostic effect is directly related to nucleic acids. The therapeutic effect can be temporary or permanent, depending on whether the nucleic acid is transiently or stably integrated within the target cell. In the case of a permanent integration, the cause of a disease can be corrected, which is particularly promising for the treatment of monogenic disorders.

In addition to somatic cell therapeutics and biotechnologically engineered tissues, gene therapeutics belong to the group of advanced therapy medicinal products (ATMP). These are either approved centrally at the European level, so that market approval can be granted in all EU member states (EC No. 1394/2007), or state-specific by way of derogation by a national approval (§ 4 (3) AMG). The central approval procedure is coordinated by the European Medicines Agency (EMA). The benefit-risk ratio is examined within the procedure involving the

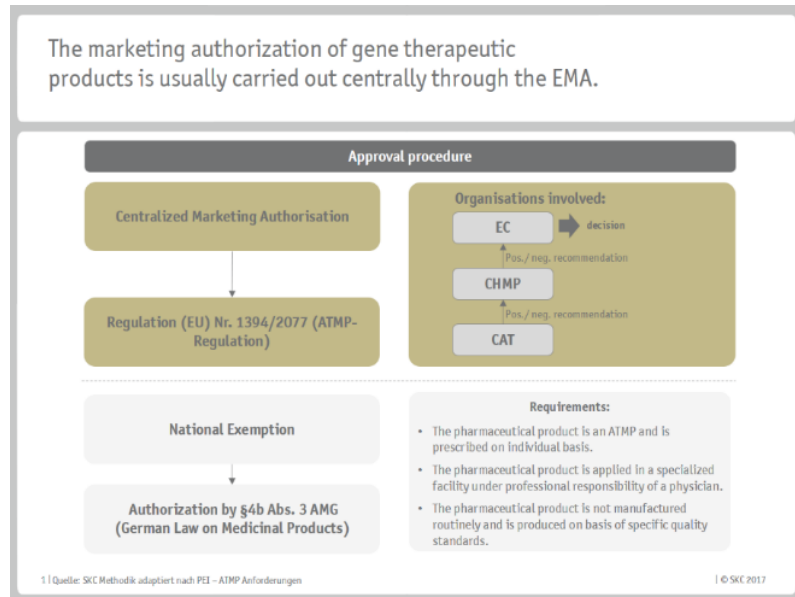


Fig. 1 Legal basis for the authorization procedures for gene therapeutics.

Committee for Advanced Therapy Medicinal Products (CAT). The CAT is responsible for the initial review and gives its approval to the Committee for Medicinal Products for Human Use (CHMP), which in turn sends a recommendation based on this to the European Commission. The European Commission finally decides on the granting of the approval. Under specific circumstances, national authorization can be obtained, provided that the ATMP is prescribed as an individual preparation by a doctor, the medicinal product is not routinely manufactured in Germany, but is manufactured according to specific quality standards, and is given in specialized institutions under the professional responsibility of a physician.

A distinction is made between *in vivo*, *ex vivo* or *in vitro* therapy. While *in vivo* therapies involve the injection of genetic material by means of a so-called vector via the blood or directly into the target cells of an individual, for *ex vivo* therapies, cells are first removed, expanded and genetically modified, and then injected back into the organism. These vectors act as a delivery tool for the genetic material and can be divided into viral (adenoviral, retroviral or adeno-associated viral (AAV)) and non-viral vectors. A further, currently extremely "hyped" procedure in gene therapy is the so-called genome editing by means of CRISPR / CAS, in which the DNA is specifically and precisely modified. By means of a so-called "guide" a pre-defined DNA sequence is

specifically found and then cut out. However, it is also possible to insert or exchange genetic material. The CRISPR / CAS system is currently under investigation in several clinical trials in the field of cancer research and ophthalmology and allows the genetic information to be incorporated more specifically into the genome.

Gene therapy can target either stem cells or somatic cells that meet certain prerequisites. Cells should have high resistance and longevity to facilitate sufficient transduction of the vector and to perform their "newly gained" function of producing the newly-gained protein over a long period of time. For *ex vivo* therapy, these cells also need to be easy to remove and re-inject into the body. Bone marrow stem cells or T cells appear to be suitable for this purpose.

### Chances and risks

Gene therapies offer the opportunity to treat diseases causatively or even to cure them. However, several risks need to be considered. Possible complications and long-term efficacy of a gene therapy are mostly unpredictable, as clinical data are currently missing. Especially as single injection, gene therapy can lead to serious complications as this type of treatment cannot be terminated or reversed. Incorporation of the vector into a random place of the genome (non-directed integration of the DNA) can interfere with cell growth or function, which amongst others might increase the risk of tumors. Specific integration of the vectors into the target cell is particularly challenging in case of an *in vivo* therapy. Selection of suitable and improved vectors is one of the main fields of research in gene therapy. *Ex vivo* therapy reduces the risk of unwanted side effects since the cellular responses (e.g. abnormal expression) can be investigated outside the body before re-introduction, thereby reducing the risk of an immune reaction of the body in response to the vector, which is likely to increase with higher vector dosages with potentially life-threatening complications. In addition, the process of vector injection into the target cell can be quite challenging due to complicated administration, especially when compared to conventional drugs (oral, subcutaneous or intravenous). The risks of surgical interventions should therefore also be

considered. Consequently, gene therapies must be carried out by specially trained and qualified specialists and medical staff.

### History of gene therapy and market overview

The earliest gene therapy trials were already carried out in the 1970s, initially restricted to monogenetic disorders of the blood and the immune system. The first gene therapy documented in a study protocol was conducted in September 1990. The patient suffered from a severe immune failure due to a rare blood disease called severe combined immunodeficiency (SCID), also known as "bubble boy disease", because patients can only survive in complete isolation from the outside, appearing like in a "bubble". This gene therapy approach was performed *in vitro* using the patient's own T cells supplied with a healthy copy of the DNA of the non-functioning native protein introduced into the nucleus. A subsequent curative effect was achieved by treatment of the blood stem cells with retroviral vectors. Gene therapy was also used for the treatment of X-linked SCID, a specific form of SCID. Unfortunately, several years after the treatment five of the patients developed leukemia, a fate shared by different patients within other clinical trials. Other serious complications were observed in several other clinical trials. These cases highlight the relevance to develop safer vectors, which play a crucial role in the evaluation of the safety of gene therapies. Second-generation retroviral vectors are based on the human immunodeficiency (HI) virus (HIV). The new design reduces complications associated with treatment. These and other improvements in vector design have made potential consequences of a gene therapeutic treatment more predictable insertion of the genetic material within the cellular nucleus. However, potential side effects remain an essential risk of the therapy.

The application of gene therapies will increase in the upcoming years, since both rare diseases and other indications open new prospects for potential treatment. Among the most frequently investigated diseases in the field of gene therapy are monogenic inherited diseases, cancer and infectious diseases. The number of clinical trials indicates the increasing relevance of this research area. Over the past two years, more than 270

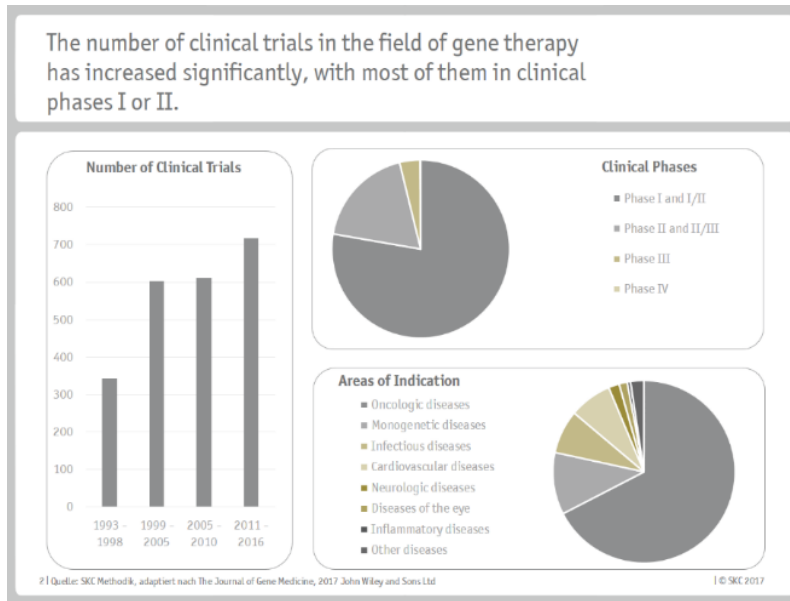


Fig. 2 Overview of the number, phases and indications of clinical trials in the field of gene therapy.

clinical trials have been initiated. More and more start-ups with the focus on gene therapy are beginning to flourish and become driving forces in this field of research.

With this, however, the question of an adequate reimbursement of gene therapies arises. Particularly for gene therapies offering a potential cure upon a one-time treatment, the current reimbursement system in Germany could quickly reach its limits. Experience in the field of reimbursement is also poor in the international context. While patients have been treated in clinical trials already for several decades, officially approved and reimbursable therapies are still an exception. Last month, the first gene therapy was approved in the U.S. which was previously recommended by an international expert panel of the American regulatory authority. Kymriah™ from Novartis is indicated for the treatment of acute lymphoblastic leukemia for approximately 750 patients in the U.S. and is estimated to cost \$ 475,000 per patients. Mydicar®, manufactured by a company formerly known as Celladone, is indicated for patients suffering from cardiac insufficiency with systolic dysfunction. Although Mydicar® was granted “breakthrough” status by the FDA in 2014, subsequent studies failed to confirm the results leading to the disapproval of Mydicar®. For further indications (see below), U.S. approval may be expected in 2018 and 2019. In Asia, gene therapies have been approved already

14 years ago. In 2003, China approved the first gene therapy worldwide based on clinical phase I / II studies. Gendicine®, from Sibiono GeneTech, offers a treatment option for patients suffering from head and neck carcinomas. Approximately \$ 400 are estimated per dosage. Detailed information on the cohort of patients treated, the efficacy or success of the treatment and the underlying reimbursement model are not available. In 2007, the Philippines followed with the approval of a gene therapy for the treatment of pancreatic cancer, but in this case further

information is difficult to get, too.

In Europe, however, a total of three gene therapies are approved: Strimvelis®, Imlygic® and Glybera®. Glybera® (Alipogen tiparvec) from Chiesi GmbH was approved by the EMA in 2012, making it the first gene therapy available in Europe. The approval process was challenging, not only due to the low number of volunteers in this study. The CHMP has discussed evidence and potential safety concerns in many consultations with the pharmaceutical company until finally a positive recommendation was given to the European Commission. In Germany, Glybera® was launched in November 2014 for the treatment of lipoprotein lipase deficiency (LPLD). Patients with LPLD are unable to process lipids properly from their diet due to the lack of lipoprotein lipase, leading to an increased level of lipids in the blood and the most severe side effect of frequent and acute pancreatitis. Glybera® utilizes an AAV vector to transport genetic material into the target cells, thus establishing LPL activity. To minimize the risk of non-directed cell growth and random integration of the genetic material, the gene is not stably integrated into the genome of the cell but instead deposited as a “mini-chromosome” in the cellular nucleus. Simultaneously to launch, the AMNOG process evaluates the additional benefit and subsequent price negotiation and reimbursement in the ambulatory sector started. At the same time, a so-called NUB process

determining reimbursement of innovative methods in the inpatient sector was initiated. While in the AMNOG process a non-quantifiable additional benefit was declared and the price negotiated with the statutory health insurance (GKV-SV) remained unpublished, reimbursement in the inpatient sector has been possible based on NUB compensation for three years. For NUB, the reimbursed sum is determined by individual negotiations between the single hospitals and the health insurance. By now, an individual supplementary fee of € 900,000 has been appointed for the only patient treated so far. This fall, Glybera® has been withdrawn from market because of low patient numbers, lack of data providing efficacy and high treatment costs. The pharmaceutical companies Chiesi, responsible for the commercialization of Glybera®, and uniQure, which developed the therapy, have terminated their collaboration.

Imlygic® (Talimogen laherparepvec) from Amgen GmbH is the second gene therapy launched in Germany and was approved by the EMA in December 2015. Imlygic® is indicated for the treatment of patients with malignant melanoma. Unlike Glybera®, Imlygic® must be injected in regular intervals (every two weeks). After the injection of the virus into the tumor, viral particles multiply and ultimately mediate the elimination of cancerous cells. In addition, a systemic immune response of the body against the tumor cells is induced by the viral injection. So far, according to the Federal Joint Committee (G-BA), no additional benefit could be demonstrated based on an open phase III clinical trial. With Strimvelis®, the first corrective gene therapy has been approved by the EMA in 2016. However, so far potential patients can only be treated exclusively in one center in Milan. Strimvelis® from Glaxo-Smith-Kline (GSK) is used to treat children with the hereditary disease ADA-SCID, which leads to severe immune deficiency ("Bubble Boy Disease"). The treatment is carried out *ex vivo*, with viral vectors being injected into previously extracted stem cells, the genetic material is integrated into the genome and the genetically modified cells are subsequently returned to the blood circulation. This procedure equips the cells in the patients' blood with the required information to produce the missing enzyme. A total of 18 children

were treated in clinical trials and observed over an average of seven years. To date, for 14 patients no further treatment is required and the effect is believed to last for a lifetime. Side effects include fever and sometimes serious autoimmune reactions. The alternative to Strimvelis® is stem cell transplantation or enzyme replacement therapy. However, Strimvelis® should only be considered if no suitable stem cell donor is available for the patient. In March 2017, the first patient was treated outside of a clinical trial, just one year after the gene therapy was approved by the EMA. The cost of a one-time treatment with Strimvelis® accounts for € 594,000, which makes the treatment one of the most expensive therapies in the world. The costs for the first patient are paid in annual installments, whereby a refund by GSK is made in case of a failure.

Currently, a promising Phase III study *in vivo* treating patients with Leber's congenital amaurosis due to an RPE-65 deficiency is currently under investigation. This rare disease of the retina can lead to blindness of the affected persons. The missing gene RPE-65 is injected into the target cells with an AAV-vector and thus eliminates the defect with a single application and the patients are cured. In contrast to other gene therapeutic approaches, only very few immunoreactions have occurred so far, while treatment showed very good efficiency. In July 2015, Spark Therapeutics received the Orphan Drug Designation from the EMA for Voretigene neparvovec and has recently submitted the Marketing Authorization Application (MAA), that might enable the treatment of patients outside of clinical trials with a commercially available product by next year. In addition, clinical trials for retinal disorders, coagulation disorders, such as hemophilia A and B as well as neurodegenerative diseases have been initiated and are relatively advanced; their approval is expected in the next two to three years. Further indications wait in the pipeline of pharmaceutical companies, which are expected to enter the market in the coming months and years. Abeona Therapeutics has developed a drug for the treatment of metabolic diseases such as the Sanfilippo syndrome, the company Alnylam prepares a total of three drugs: Patisiran for the treatment of the ATTR-Amyloidosis, Fitusiran for the treatment of hemophilia and Givosiran for the

treatment of acute hepatic porphyria. Bluebird Bio, another U.S. company has set the focus on the treatment of  $\beta$ -thalassemia.  $\beta$ -thalassemia is a hereditary disease characterized by a disturbed production of hemoglobin due to a mutation in the globin genes. Patients are in need of live-long transfusions, but could be cured by the injection of blood stem cells that had been modified *ex vivo* to express the beta-globin genes. UniQure is also focusing on the gene therapy for the treatment of patients suffering from hemophilia B, which received "breakthrough" status from the FDA in January 2017.

### The reimbursement dilemma

Although the development of new gene therapies for incurable and / or very rare genetic diseases has only begun, successes in clinical trials are impressive and without exaggeration we can call out a new era of medicine. The first approvals in Europe have paved the way for those upcoming therapies. Gene therapy is happening now and is entering the medical standard care. Potentially increasing numbers of such therapeutic options are a further important step in clinical research and holds out the prospect of a potential success for patients in currently hopeless situations. For the reimbursement of gene therapies, especially therapies for which a single administration of vector is sufficient, the previous reimbursement models do not seem to be adequate. The existing reimbursement system for new drugs in Germany is generally separated in the outpatient and in-patient sectors. The potential cure of a disease by gene therapy would currently be covered like a one-time reimbursement of the drug (at the time of administration). At that time, the respective health insurance would have to reimburse the full amount of the negotiated reimbursement to the pharmaceutical company, although the efficacy and safety of the gene therapy will be visible only after the treatment. This is associated with a high risk for the payers. The system of advance payments is a challenge that does not occur with conventional treatment options. Reimbursement of a permanent or temporary treatment has the advantage of patients being able to discontinue treatment in case of lacking effectiveness or occurring side effects and permits a switch to newly approved, more effective pharmaceuticals.

Reimbursement therefore only occurs during this clearly defined period in which the therapy is beneficial for the patient. An advance payment, as in the case of a once-applied gene therapy, means that the health insurance has to reimburse the full amount before and not during the therapy, although the cost-effectiveness is usually not yet evaluated. Possible cost savings or an amortization due to the no longer necessary treatment can often only be achieved years after the actual treatment. This results in a late and uncertain break-even for the health insurance companies. In addition, free selection of health insurance by the insured patients does not guarantee that the financing health insurance company can profit from the counter-financing or amortization effect, since the patient can change to a different insurance as a now healthy person. There is no specific compensation mechanism for the imbalance of costs and benefits between different payers. In the case of private health insurance, this problem does not exist in this form due to the severely restricted or non-existing switching options.

High-priced pharmaceuticals such as Soliris<sup>®</sup> or Vimizim<sup>®</sup> can also cost insurance companies a seven-digit amount for a single patient over a period of several years, however, the budget impact is distributed differently, as the costs do not only occur once but are spread out over time. This situation creates a controversy, especially in the inpatient sector, as the life-long benefit is contrasted by annual budget negotiations. Current gene therapies are high-priced drugs and subsequent therapies are likely to be as costly due to the high degree of innovation and the rarity of the diseases. The treatment with Glybera<sup>®</sup> was charged over € 1 million in the ambulatory area, while Strimvelis<sup>®</sup> is estimated to cost approximately € 600,000. However, the uncertainty about the effectiveness and safety of the treatment is high due to the lack of precedents and long-term observations, so that the high prices can appear unjustified from perspective of the payers.

The dilemma evolves between the price expectations of the pharmaceutical companies, which need to cover their advanced costs for research and development, as well as the need to secure their revenues through the one - time sale

of the product, and the concerns of the respective health insurance companies which do not have a guarantee on efficiency and safety of the treatment, as well as on the opportunity to amortize the high costs of such therapies. To counteract this dilemma, new and innovative and flexible reimbursement models need to be developed, thus ensuring that patients in Germany have access to innovative and highly effective therapies. Particularly in the case of diseases for which alternative, non-curative treatments are available, the payers' concerns can be extremely high.

### Alternative reimbursement options

For many rare and some very severe diseases, such as life-threatening diseases, an extremely high unmet need for curative therapeutic options remains. This unmet need not only increases the willingness to approve access of treatments to the market even with lower evidence levels, but from a social perspective it also increases the willingness to pay.

While retaining the existing logic, an appropriate reimbursement could be established based on methodologically developed health economic models that would allow the assessment of a (lifetime) benefit and effectiveness. Thus, a long-term or lifelong effect has to be assumed of which monetarized benefits are discounted at the time of intervention. In addition, the degree of innovation of such therapies could be considered within the reimbursed amount. Within the approval process, the pharmaceutical company already has to be able to dispel any (serious) safety concerns through clinical data and provide evidence of the efficacy of respective products. This evaluation of the benefit - safety profile is once again confirmed by the AMNOG procedure which is geared to the German care context. The challenge is to provide evidence which proves significant benefit of the new therapy. The mostly limited number of patients as well as the lack of comparable therapies with other agents and validated patient-relevant endpoints in addition to the limited duration of these studies, might lead to a high bias potential and thus to increased uncertainty in the assessment of the benefit and damage potential. An early collection of data by the establishment of patient registers therefore

seems indispensable in this field to render the companies able to prove the success of the therapies in the long term or to be able to prove former hypotheses about the future benefit.

Furthermore, the financing model of Strimvelis® could be a possibility for a future reimbursement of gene therapies in Germany. Roughly one year passed from the beginning of approval to negotiation and reimbursement of the first treatment. Within the procedure, an annuity-based model was linked to the pay-for-performance approach in form of an installment payment of the reimbursement amount. This model was coupled with a money-back guarantee in the event of failure. The idea of an annuity-based reimbursement model is to distribute the costs over a *defined* time period. This means that the reimbursement amount is not completely refunded at the time of the treatment, but instead disbursed in rates over a period of several years. The reimbursement can be linked to the long-term effectiveness of the therapy so that the risk or the uncertainty of the efficacy of the gene therapy is shared between the pharmaceutical company and the payer. However, there are some obvious challenges. For one, there is the measurement of effectiveness. In this context, patient-relevant endpoints could be used, which, however, are often not sufficiently validated or accepted, in particular for rare diseases. Moreover, these endpoints have to be determined on an individual basis for each therapy. In addition, the number of relevant endpoints must be defined carefully. When selecting several endpoints, it should also be determined which endpoints have to be significant to which extent and at which timepoint. Regarding reimbursement, the amount of the partial payment can also be varied. Depending on data or type of therapy, it may be reasonable to reimburse higher amounts at the beginning or at the end of the therapy or to determine a constant amount over the entire period. This can occur depending on the predicted effect or also on potential long-term damage. One variant of this model is to reimburse the entire amount at the beginning and to agree on a payback from the pharmaceutical company to the payer, depending on the effectiveness of the therapy. Here, as well, the above-mentioned points must be defined and agreed in advance.

Primarily, this approach appears practical, but is dependent on very individual solutions. For this purpose, general criteria should be laid down for establishing the model to create a formal framework. This allows for a flexible yet standardized solution. Furthermore, long-term follow-up of the patients calls for establishment of patient registries, thereby allowing a better assessment of the care situation. Both approaches, the assessment of reimbursement based on the validated benefit as well as the distribution of costs over a longer period of time, do not solve the problem of the lack of amortization of the expenses made in case of the insured patients changing the insurance company. This can only be achieved through collectivization, for example an adaptation of the morbidity-oriented risk-compensation mechanism (morbi-RSA), such as the reintroduction of the so-called high-risk pool, which could cover specific gene therapy interventions. This solution using funds could also be organized privately as an intermediary incorporation whose risk is covered by a reinsurance. As a result, the initial costs would be collectivized and insured so that the insured's freedom of choice would not have to be restricted and the fund or pool would balance the expenses and amortization. Likewise, in the event of failure, where the promise of life-long healing is not kept, the fund could cover a new therapy, respectively. The actuarial calculation of the compensation mechanisms, the inclusion and exclusion criteria as well as the derived bonus is highly demanding, though, and should be carried out and simulated based on existing data in order to develop different models and test them for sustainability.

### Conclusion

Gene therapy will emerge from the experimental stage in the immediate future and will become a clinical standard beyond a few rare diseases. The value proposition of the therapeutic approaches is to achieve a curative effect with a one-time application. The high expense, particularly the very high costs, will then only occur once and lead to a significant reduction in the cost of a chronic disease that otherwise is to be paid lifelong. Nevertheless, this amortization mechanism cannot be realized in a pay-as-you-go system of contribution by cameralistic entities using the established instruments, particularly in terms of a potential switch of the gene therapy-treated patient from one insurance to another. Since many gene therapeutical drugs will be approved in the next 2-3 years, promising a high degree of efficacy in clinical data, it seems necessary that, in particular, the statutory health insurers immediately develop financing and reimbursement models that meet the cost mechanisms of gene therapy, with the result that promising therapies can be made accessible to the severely sick patients in Germany. The developed solutions should be a practicable compromise for all stakeholders within the system; thus, primarily reducing the uncertainty of the payers and to continue giving manufacturers incentives to develop innovative treatment options.

### References

Comprehensive literature and references can be obtained from the authors.