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Statement of the DOG, the RG, and the BVA on the therapeutic use of voretigene neparvovec (Luxturna™) in ophthalmology. English version

January 2019

Luxturna™ was approved in the European Union for the treatment of retinal dystrophy in patients with biallelic *RPE65* mutations and sufficient viable retinal cells on 23 November 2018. The following article presents the treatment recommendations for Luxturna™ (Novartis, Basel, Switzerland) formulated on the basis of a consensus between the German Retina Society, the German Ophthalmological Society, and the German Professional Association of Ophthalmologists.

1 Key messages of the statement

All of the following conditions should be met prior to performing treatment with Luxturna™:

- The diagnosis of retinal dystrophy has been clinically confirmed. Grade of recommendation: ↑↑
- Biallelic (homozygous or compound heterozygous) sequence variants in the *RPE65* gene have been identified as the cause of disease. Ideally, identification is performed by means

of segregation analysis in the parents.

Grade of recommendation: ↑↑

- It has been established that sufficient target cells are available to ensure a therapeutic benefit. Grade of recommendation: ↑↑
- The patient, and where appropriate their legal guardian(s), has (have) been individually informed about the natural course of the disease, the prognosis of the planned treatment, the risk profile of the treatment, as well as other possible treatments. Grade of recommendation: ↑↑
- There are no data available on the safety and efficacy of Luxturna™ treatment under the age of 4 years. Grade of recommendation: Statement

All of the following conditions should be met to optimize outcomes with Luxturna™ treatment:

- Experience of vitreoretinal surgery in children and young adults. Grade of recommendation: ↑↑
- Experience of subretinal surgery in patients with advanced retinal dystrophy or other degenerative retinal disorders. Grade of recommendation: ↑↑

- The accumulation of Luxturna™ in the vitreous cavity, and hence the risk of lower bioavailability in the target tissue and/or greater systemic distribution, should be avoided. Grade of recommendation: ↑↑
- Concomitant anti-inflammatory medication should be prescribed according to the product information. Grade of recommendation: ↑↑
- The interval prior to treatment of the contralateral eye should be planned according to the product information. Grade of recommendation: ↑↑

The use of intraoperative optical coherence tomography (OCT), as well as a vitrectomy system with semi-automated injection speed controlled by the surgeon enables the verification of subretinal injection of Luxturna™ under controlled conditions. Grade of recommendation: Statement.

All of the following technical conditions need to be met for the performance of Luxturna™ treatment:

- Formal education has been provided by the manufacturer in the preparation and surgical administration of

The German version of this article can be found under <https://doi.org/10.1007/s00347-019-0885-3>.

Luxturna™. Grade of recommendation: ↑↑

- The equipment required for the correct storage and preparation of the injection solution is available. Grade of recommendation: ↑↑
- The active substance and solvent are stored at temperatures below -65°C up to the time of use and the cold chain is maintained. Grade of recommendation: ↑↑
- The preparation of Luxturna™ for administration takes place using aseptic technique and under sterile conditions by trained personnel according to the dual control principle. Grade of recommendation: ↑↑
- The entire surgical team is trained in handling biosafety level 1 agents. Grade of recommendation: ↑↑
- Administration complies with the specifications of the manufacturer or the company distributing the product. Grade of recommendation: ↑↑
- Disposal of the virus suspension as well as surface disinfection in the operating theater is carried out according to the relevant regulations and the current recommendations of the Robert Koch Institute. Grade of recommendation: ↑↑

All of the following conditions should be met as part of the follow-up of patients after Luxturna™ treatment:

- All side effects are documented in a registry study. Grade of recommendation: ↑↑
- The treatment of complications is performed by the initial treating physician and/or with their involvement. Grade of recommendation: ↑↑
- The clinical examination and testing of visual function are carried out under standardized conditions. Grade of recommendation: ↑↑
- At the very least, best corrected visual acuity, full-field stimulus threshold testing (FST) as well as OCT and fundus autofluorescence (FAF) imaging should be performed preoperatively and in the postoperative course to assess treatment success. Grade of recommendation: ↑↑

2 Foreword

Gene therapy represents a completely new form of treatment. Based on numerous basic scientific and preclinical studies, clinical trials with gene therapy products show the potential to treat previously incurable ophthalmological diseases. To date, however, only one evidence level Ib study has been published on the efficacy of gene therapy for the eye. All other randomized controlled studies have either not been completed or are not yet published. As such, no systematic, evidence grade 1a review article is available as yet.

2.1 Introduction to gene therapy of retinal dystrophy due to biallelic mutations in the RPE65 gene

Gene therapy refers to the introduction of a therapeutic nucleic acid into the affected cells of a patient [2, 3]. In the case of gene therapy with Luxturna™, a single-strand DNA molecule with the coding sequence (cDNA) of the RPE65 gene (and other regulatory elements) is used. The cDNA codes for the RPE65 enzyme, which, due to biallelic mutations, is either not produced by the cell itself before treatment or, at best, only in small quantities or with reduced functionality. In the case of biallelic mutations in the RPE65 gene, this reduction in RPE65 enzyme activity results in reduced or absent visual cycle activity [4]. RPE65 usually regenerates 11-*cis*-retinal, thereby ensuring a functioning retinal/retinol cycle: upon light absorption in the outer segments of the photoreceptor, 11-*cis*-retinal is initially converted to all-*trans*-retinal, which is then reduced to all-*trans*-retinol in the outer segment. In the retinal pigment epithelium (RPE), all-*trans*-retinol is converted back to 11-*cis*-retinal with the help of a number of enzymes (e.g., RPE65) and is once again available to the photoreceptor for the production of light-sensitive photopigment together with cell-specific opsin.

The rods are 100% dependent on the visual cycle described above, whereas the cones can to a certain extent fall back on 11-*cis*-retinal from other sources (from the rods themselves or from Müller cells).

Therefore, the loss of RPE65 enzyme function affects the rods in particular (early night blindness in patients), while the cones often exhibit a certain degree of functionality, at least in the early stage of disease [5]. Varying levels of residual enzyme activity are responsible for the differences in severity of the disease phenotype, as a result of which a number of different clinical diagnoses were made in the past (Leber congenital amaurosis [LCA], early-onset severe retinal dystrophy [EOSRD], retinitis pigmentosa [RP], etc. [6, 7]).

The correct cDNA of the RPE65 gene, together with other regulatory DNA sequences (e.g., promoter, poly-A sequence), is introduced using recombinant adeno-associated viral (AAV) vectors from which virtually all viral DNA has been removed and which, due to their serotype-dependent cellular tropism, are particularly suitable for gene transfer into RPE and photoreceptors. In the case of Luxturna™, a recombinant serotype-2 AAV is used.

By introducing the correct cDNA of the RPE65 gene, the patient's treated RPE produces the functional RPE65 enzyme, which then generates 11-*cis*-retinal as part of the visual cycle. By transporting the remaining photoreceptors into the outer photoreceptor segment, light-sensitive photopigment is generated and the phototransduction cascade initiated following light exposure [8]. It is currently assumed that those photoreceptors whose function is restored do not undergo further degeneration [9–11].

Thus, the aim of gene therapy using voretigene neparvoec is to improve visual function and prevent the natural course of disease. This specific form of gene therapy was first performed on patients in 2007 [12] and was approved by the US Food and Drug Administration (FDA) in 2017 and by the European Medicines Agency (EMA) at the end of 2018.

Further review articles on the therapeutic strategies available in gene therapy have been published in German in *Ophthalmologie* [2] as well as the *Zeitschrift für praktische Augenheilkunde* [13]. The psychological status of patients in light of the

possibility of gene therapy was discussed in an article by Nelles and colleagues [14].

The following article discusses establishing the indication (clinical and molecular genetic diagnostic methods and the identification of target tissue) and the surgical performance of gene therapy as well as its follow-up.

2.2 Indication for treatment with Luxturna™

According to EMA guidelines, gene therapy with Luxturna™ is indicated in all patients fulfilling the following three criteria:

1. Clinical diagnosis of retinal dystrophy
2. Biallelic *RPE65* gene mutations confirmed by molecular genetic testing
3. Clinical evidence of viable retinal tissue as the target of gene therapy

2.2.1 Clinical diagnosis of retinal dystrophy

The approval trial did not specify any criteria for the clinical diagnosis of retinal dystrophy [1]. The clinical diagnosis of retinal dystrophy should be made by an ophthalmologist with experience in the field of hereditary retinal dystrophies. Centers specializing in the diagnosis of these disorders are particularly worthy of note here.

It is important to emphasize that all variations of the clinical picture of retinal dystrophies (e.g., LCA, EOSRD, RP) due to *RPE65* deficiency can be considered for treatment. This is due to the fact that it is not the clinical classification of the disorder that is crucial to Luxturna™'s mode of action, but rather the disease-causing mutations on both alleles of the *RPE65* gene.

Taking a formal family history is recommended as part of the clinical diagnosis. In general, the clinical diagnosis is then confirmed by means of the following investigations [15–18]:

- Full-field electroretinography (ERG; International Society for Clinical Electrophysiology of Vision [ISCEV] standard)
- Perimetry

- Optical coherence tomography (OCT)
- Fundus autofluorescence (FAF)

2.2.2 Molecular genetic diagnostic methods

Patients with biallelic mutations in *RPE65* were treated in the approval trial, but no further criteria for molecular genetic diagnosis were defined [1]. Molecular genetic diagnosis should be performed by a certified laboratory and the results made available to the patient or legal guardian in the setting of genetic counseling. Since not all sequence variants in a gene are pathogenic, causality should be investigated by appropriately qualified personnel (human geneticist, specialist physician for human genetics, or physician with an additional title in medical genetics). Two criteria need to be fulfilled in the assessment of whether a patient is suitable from a genetic perspective for gene therapy with Luxturna™:

- Confirmed biallelism
- The mutations should generally be classified as likely pathogenic or pathogenic variants when applying the classification system of the American College for Medical Genetics and Genomics (ACMG).

Confirmation of biallelism in formal genetics generally requires both parents to be tested (segregation analysis), both for homozygotic and heterozygotic mutations. Mutations categorized as benign variants of no clinical significance, likely benign variants, or variants of uncertain significance (VUS) are not by themselves sufficient to establish the indication for gene therapy with Luxturna™. Interestingly, patients with mutations that were considered VUS from a formal genetics perspective were treated in the approval trials (Ohnsman et al., Annual Meeting of the American Academy of Ophthalmology 2018). As such, the available evidence does not enable a conclusive assessment of whether only patients with mutations classified as likely pathogenic or pathogenic variants benefit from treatment with Luxturna™. It is currently not possible to clearly define the indication

in patients with sequence variants of uncertain clinical relevance.

2.2.3 Identifying target tissue

The cells of the RPE are the primary target of treatment with voretigene neparvovec. The aim of treatment is to confer diseased RPE cells with the ability to produce retinoid isomerohydrolase RPE65. This enzyme enables the conversion of 11-*trans*-retinal to 11-*cis*-retinal. 11-*cis*-retinal is the light-sensitive component of the photopigment (apo-rhodopsin + 11-*cis*-retinal in rods) and is made available by the RPE to the photoreceptors for reuse in phototransduction. Thus, this important step in vitamin A metabolism, involving an interaction between RPE and photoreceptors, results in sustained light sensitivity of the retina and thereby an improvement in visual function. Conversely, this means that, for treatment with Luxturna™ to be successful, RPE cells as recipients as well as photoreceptors and downstream retinal neurons need to be present in order to make an improvement (or restoration) of visual function likely. EMA approval leaves the assessment of retinal cell viability to the discretion and experience of the treating physician to assess whether functional retinal tissue is still present, without providing any clear criteria.

The approval trial [1] defined the following three alternative criteria for identifying functional retinal tissue:

- I. Total retinal thickness of >100 µm at the posterior pole
- II. A residual island in the central (30°) visual field (isopter III-4e)
- III. An area without atrophy of at least three disc diameters

On (I): The identification of >100 µm total retinal thickness at the posterior pole should be viewed critically, since no differentiation is made between inner and outer retina. Therefore, total retinal thickness alone is not suitable for the assessment of whether a functionally relevant number of RPE cells and photoreceptors are present in such a way that makes a treatment effect likely.

On (II): The perimetric detection of a residual island in the central 30° is also to be viewed critically, since a finding

of this kind in the presence of nystagmus can only be reproduced to a limited extent. In addition, potentially valuable residual islands outside the central 30° are not taken into consideration in everyday routine.

On (III): The third criterion was used in the approval trial primarily for the inclusion of young children in whom examination by means of OCT or perimetry was not feasible. However, in the opinion of the authors, the funduscopy performed to this end is not a sensitive method to exclude outer retinal atrophy.

The correlation between structure of the outer retina and visual function is well documented in patients with *RPE65* mutations [19]. Therefore, detection of an outer nuclear layer (ONL) should serve as structural evidence. If detection of a defined ONL is not possible, e.g., due to marked nystagmus, functional residual tissue needs to be reliably detected using standardized functional tests¹.

A good method to demonstrate the presence of both cell populations (RPE and photoreceptors) and their functional interaction is to measure light sensitivity by means of full-field stimulus threshold (FST) testing. White light was used to this end in the approval trial. Although this protocol is highly sensitive and does not rely on fixation, it does not differentiate photoreceptor classes, and it appears at least possible that intrinsically photosensitive retinal ganglion cells (ipRG) also take over perception in the absence of the outer retina (RPE and photoreceptors). However, additional FST tests with blue and red light are able to demonstrate rod function in a specific manner from the difference in dark-adapted threshold values [20–23]. Treatment with Luxturna™ is not recommended in the absence of functional or structural evidence of viable residual tissue.

Failure to respond to ERG is a typical finding in patients with *RPE65*-associated retinal dystrophy [24] and does not necessarily mean that rod and/or cone

function is no longer present. Therefore, an ERG signal that cannot be measured does not represent grounds to rule out treatment with Luxturna™.

2.3 Performing retinal gene therapy with voretigene neparvovec-rzyl

Subretinal gene therapy with Luxturna™ should only be carried out in centers with appropriate equipment for the proper storage and preparation of the injection solution, as well as experience in vitreoretinal surgery in children and young adults. Centers should have previous experience of subretinal surgery in patients with advanced retinal dystrophy or other severe degenerative disorders of the central retina. If children are treated, an anesthetist with experience in pediatric anesthesia should be available, as should the option for postoperative monitoring on a pediatric unit at the treating institution in the event of complications.

Administration is performed in compliance with the specifications of the manufacturer or the company distributing the product. The manufacturer's specifications for the EMA-approved product describe administration via retinal injection of 0.3 ml of the vector suspension (dose 1.5×10^{11} vector genomes [vg]) using pars plana vitrectomy (e.g., 23 G or 25 G) followed by air tamponade. An interval of no fewer than 6 days is recommended before treatment of the contralateral eye.

The EMA has stipulated that the manufacturer provide education on the preparation and administration of Luxturna™ as part of a risk-management program. Participation in education of this kind is mandatory prior to use on the patient.

2.3.1 Vector preparation

The active substance in Luxturna™ consists of a recombinant adeno-associated virus (AAV) with a therapeutic gene sequence that enables RPE cells to produce the retinoid isomerohydrolase RPE65. The AAV are approximately 25 nm in size and are stable in aqueous solution. However, the active substance should be stored at temperatures below -65°C up to the time of use, and the cold chain should be maintained and documented.

Luxturna™ can be prepared for administration 4 h prior to treatment at the earliest. This should be carried out using aseptic technique and under sterile conditions in a class II microbiological safety cabinet. The instruments and materials required to prepare Luxturna™ for administration to the patient are available in an ophthalmology surgical center. Compliance with the requirements of the German Genetic Engineering Act (*Gentechnikgesetz*, GenTG) and safety measures when performing genetic engineering activities in genetic engineering facilities (German genetic technology safety regulations; *Gentechnik-Sicherheitsverordnung*, GenTSV) is mandatory.

It is recommended that the preparation of Luxturna™ be carried out by trained personnel according to the dual control principle. Personnel should be trained in handling biosafety level 1 agents and in working with a safety cabinet (see above). Specific standard operating procedures (SOPs) for the reconstitution and disposal of waste products are recommended in order to ensure compliance with the manufacturer's stipulations as well as all safety requirements. The sterility of the virus suspension needs to be ensured during preparation and transportation to the operating room.

2.3.2 Administration of the vector

All instruments and materials required for the administration of Luxturna™ should be available at the surgical center (e.g., 41-G injection cannula). The entire surgical team should be trained in handling biosafety level 1 agents. The surgeon should have experience in subretinal surgery and in the vitreoretinal surgical treatment of children. Ideally, the surgeon is experienced in the ophthalmic surgical treatment of patients with retinal dystrophy.

The use of a surgical microscope with intraoperative OCT is recommended, as is the use of a vitrectomy system that enables the surgeon to control the rate of vector injection [25]. Intraoperative OCT enables a differentiation to be made between suprachoroidal, subretinal, and intraretinal fluid. Thus, accidental administration in the suprachoroidal in-

¹ If not all functional tests can be carried out in a reproducible manner in young children (3–6 years) but an ONL cannot be adequately detected, one can assume that functional residual tissue is present [9].

Table 1 Ocular side effects following treatment with Luxturna™ (n = 41) in the approval trial [1]

Side effects	Study participants (n = 41)	Eyes treated (n = 81)
Total of all ocular side effects	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Elevated intraocular pressure	6 (15%)	8 (10%)
Retinal hole	4 (10%)	4 (5%)
Corneal dellen	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits ^a	3 (7%)	3 (4%)
Inflammation of the eye	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Ocular pain	2 (5%)	2 (2%)
Epiretinal membrane	2 (5%)	3 (4%)
Foveal atrophy with central scotoma	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal schisis	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

^aTransient and asymptomatic accumulation of precipitates under the retinotomy 1–6 days following injection

stead of the subretinal space can be avoided and the localization and extent of subretinal injection can be objectively identified. Intraocular administration of the vector outside the subretinal space has unfavorable sequelae in terms of both the therapeutic effect (lower bioavailability in the target tissue) and the risk profile (greater systemic biodistribution) [26, 27]. Therefore, it may be beneficial prior to the injection of Luxturna™ to first open the potential subretinal space with a buffered electrolyte solution (e.g., balanced salt solution [BSS]). Luxturna™ can then be administered through the initial retinotomy. Subsequent fluid–air exchange is recommended in order to eliminate any potential virus particles in the vitreous cavity. Care should be taken here to avoid performing aspiration near the retinotomy. Depending on the individual case, the surgeon decides whether sclerotomies need to be sutured and/or whether air tamponade is required.

Disposal of the virus suspension as well as surface disinfection in the operating room should comply with local regulations. Current publications by the Robert Koch Institute on the efficacy of disinfection agents for non-enveloped viruses are essential to this end (<https://www.rki.de/DE/>

[Content/Infekt/Krankenhaushygiene/Desinfektionsmittel/Virusinaktivierung/Aufber_Medizinprod_FAQ_07.html](#)).

Concomitant medication. Concomitant anti-inflammatory medication is prescribed according to the product information. Prednisolone (1 mg/kg body weight per day, but not to exceed 40 mg/day) over 7 days in total (beginning 3 days prior to voretigene neparvovec administration), followed by a stepwise reduction in the maximum dose over 10 days (unless the second eye is to be treated within this period at which point the original regime supersedes the tapering). This systemic treatment should be combined with conventional local treatment for vitrectomized patients (e.g., eye drops with steroidal or non-steroidal anti-inflammatory drugs and antibiotics).

Treatment of the contralateral eye. The EMA recommends an interval of no fewer than 6 days prior to treatment of the

contralateral eye². This recommendation is based on the results of the approval trial [1] as well as a previous safety study [28] and general immunological findings [29] on the immune response of the eye to viral vectors. Although the EMA has not made any clear recommendations in this regard, it also makes reference to the approval trial.

2.4 Follow-up of treatment with voretigene neparvovec

The aim of follow-up is to identify complications requiring treatment (e.g., endophthalmitis, ocular hypertension, retinal hole, vitreous hemorrhage, cataract) and is therefore guided by the relevant protocols on the follow-up of age-appropriate vitrectomy patients (see **Table 1** for the range of side effects seen in clinical studies).

A further goal of follow-up is to test and document the improvement in visual function or the preservation of visual function in the long term. Visual functions that underwent significant improvement in the approval trial included orientation and mobility at low light levels (multi-luminance mobility testing, MLMT) and retinal sensitivity as measured by the FST [1]. Improvements in visual function were most pronounced in the 2-week to 6-month period and, in some cases, could still be demonstrated at 5 years [1, 30–32].

Based on this evidence, postoperative functional testing should at the very least include measurement of best-corrected visual acuity and total retinal sensitivity (FST). Quantitative mobility testing (MLMT), as well as standardized pupillometry and fundus-controlled perimetry are recommended functional tests. OCT and FAF are recommended as morphological examinations.

As part of their risk management program mentioned above, the EMA re-

² https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&ved=0ahUKEwj1IsiF0eHbAhVJa1AKHdK8BaYQFghGMAM&url=https%3A%2F%2Fwww.fda.gov%2Fdownloads%2FBiologicsBloodVaccines%2FCellularGeneTherapyProducts%2FApprovedProducts%2FUCM589541.pdf&usq=AOvVaw1_at1pmgJyPsqjIwnhOqN6.

quires all patients treated with Luxturna™ to be registered in order to investigate the treatment's safety and efficacy over a 5-year period. Details on the scope of investigations to be conducted here are not known as yet.

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Compliance with ethical guidelines

Conflict of interest See Table 2 in the appendix.

This article does not contain any studies with human participants or animals performed by any of the authors.

The supplement containing this article is not sponsored by industry.

Appendix

Table 2 Information on conflicts of interest										
	1	2	3	4	5	6	7	8	9	10
	Consultancy, expert opinion, or paid employment in a scientific advisory board of a company in the health industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract institution, or an insurance company	Fees for lecture and training activities or paid authorships or co-authorships on behalf of a healthcare company, a commercially oriented contract research organization, or an insurance company	Financial contributions (third-party funds) for research projects or direct financing of employees of the institution by a healthcare company, a commercially oriented contract research organization, or an insurance company	Owner interest in medical products (e.g., patent, copyright, sales license)	Ownership of shareholdings, shares, funds with participation of companies in the healthcare industry	Personal relationships with an authorized representative of a company in the health industry	Member of relevant professional societies/associations in connection with the development of guidelines, mandate holder in the context of the development of guidelines	Political, academic membership of certain "schools", scientific, or personal interests that could give rise to possible conflicts	Current employer, relevant previous employers of the last 3 years	Consultancy, expert opinion, or paid employment in a scientific advisory board of a company in the health industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract institution, or an insurance company
Agostini, Prof. Dr. Hans	Yes Novartis, Bayer, Roche, Allergan, Zeiss	Yes Novartis, Allergan, Zeiss	Yes Novartis	No	No	No	Yes DOG, RG, BVA	No	Eye Center at Medical Center, University of Freiburg	No
Bertram, Prof. Dr. Bernd	No	No	No	No	No	No	Yes President of the BVA, member of the DOG Executive Board, Speaker of the DOG-BVA-Guideline Commission	No	Self-employed ophthalmologist	No
Fischer, Prof. Dr. Dominik	Yes Consultancy services for Nightstar Therapeutics, Eye-Serve, Horama, Sanofi, Adelphi Values, Novartis, Bayer, Casebia Therapeutics	Yes Nightstar Therapeutics, Novartis, Bayer	Yes Third-party funds for research intentions from Nightstar Therapeutics, Novartis, Bayer, Casebia Therapeutics	Yes Patent for treatment of retinitis pigmentosa (# 201847008540, Oxford University Innovation Limited)	No	No	Yes DOG, RG, ARVO	No	University Eye Hospital, Tübingen University Hospital	No

Table 2 (Continued)

	1	2	3	4	5	6	7	8	9	10
Herrmann, Dr. Philipp	Consultancy, expert opinion, or paid employment in a scientific advisory board of a company in the health industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract institute, or an insurance company	Fees for lecture and training activities or paid authorships or co-authorships on behalf of a healthcare company, a commercially oriented contract research organization, or an insurance company	Financial contributions (third-party funds) for research projects or direct financing of employees of the institution by a health care company, a commercially oriented contract research organization, or an insurance company	Owner interest in medical products (e.g., patent, copyright, sales license)	Ownership of shareholdings, shares, funds with participation of companies in the health-care industry	Personal relationships with an authorized representative of a company in the health industry	Member of relevant professional societies/associations in connection with the development of guidelines, mandate holder in the context of the development of guidelines	Political, academic membership of certain "schools", or scientific, or persons that could give rise to possible conflicts	Current employer, relevant previous employers of the last 3 years	Consultancy, expert opinion, or paid employment in a scientific advisory board of a company in the health industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract institute, or an insurance company
Keller, Prof. Dr. Ulrich	Yes Grünenthal GmbH, Roche GmbH	Yes Allergan, Bayer, Novartis Yes Heidelberg Engineering GmbH, Novartis, Bayer Vital GmbH	No Yes Bayer Vital GmbH, Mylan Ltd., Novartis GmbH, Samsung GmbH, Roche GmbH	No	No	No	Yes DOG	No	Univ. Augen-klinik Bonn MVZ Augengärztliches Diagnostik- und Therapiezentrum Siegburg GmbH	No
Lorenz, Prof. Dr. Birgit	No	Yes Novartis GmbH, Spark Therapeutics USA, Bayer Vital GmbH	No	No	No	No	Yes DOG, RG, BVA, ARVO	No	Justus Liebig University Gießen, University Hospital of Gießen and Marburg, Gießen campus	No

DOG German Society of Ophthalmology, RG German Retina Society, BVA Professional Association of German Ophthalmologists, ARVO Association for Research in Vision and Ophthalmology

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