Der Ophthalmologe

Leitlinien, Stellungnahmen und Empfehlungen

Ophthalmologe
https://doi.org/10.1007/s00347-019-0889-z

Professional Association of German Ophthalmologists (Berufsverband der Augenärzte Deutschlands e. V., BVA)[1] · German Society of Ophthalmology (Deutsche Ophthalmologische Gesellschaft, DOG)[2] · German Retina Society (Retinologische Gesellschaft e. V., RG)[3]

[1] Professional Association of German Ophthalmologists (Berufsverband der Augenärzte Deutschlands e. V.), Düsseldorf, Germany

[2] German Society of Ophthalmology (Deutsche Ophthalmologische Gesellschaft), Munich, Germany

[3] German Retina Society (Retinologische Gesellschaft e. V.), Freiburg, Germany

Statement and supplementary statement from the BVA, the DOG, and the RG on laser treatment of drusen in age-related macular degeneration (AMD)

August 2017, update October 2018

Statement from the BVA, the DOG, and the RG on laser treatment of drusen in age-related macular degeneration (AMD)—August 2017

Key messages

- **Although conventional laser coagulation of drusen in age-related macular degeneration (AMD) results in their regression, it does not, according to current knowledge, reduce the risk of AMD progression and should therefore not be performed.**
- **Newer "micropulse" and/or "subthreshold laser techniques" are still undergoing clinical trials for early and intermediate dry AMD (in the absence of geographic atrophy). There is currently insufficient scientific evidence to conclusively assess the efficacy of these techniques in AMD.**
- **At present, no form of retinal laser treatment for dry AMD should be performed outside of clinical trials.**

The German version of these articles can be found under https://doi.org/10.1007/s00347-017-0574-z and https://doi.org/10.1007/s00347-018-0834-6.

Background

AMD is a retinal disorder associated with deposits of extracellular debris (drusen) and pigment changes in the retina [1]. It progresses from early to intermediate and on to late AMD over, on average, 10 years [1]. Early and intermediate stages are mostly associated with minor symptoms if any, whereas a significant loss of visual acuity and central visual field occurs at later stages.

There is as yet no specific treatment for early and intermediate AMD that is able to either slow down or stop progression or cure the disease at this stage. However, the supplementation of high-dose antioxidant supplements (Age-Related Eye Disease Study [AREDS] medication) in pronounced early AMD (AREDS stages 3 and 4; see Statement of the Professional Societies on AREDS [1, 2]) has been shown to slow down and prevent progression to late stage exudative disease and can therefore be recommended for this level of severity of early AMD.

Mode of action of laser coagulation on the retina

Hypothesis

Laser treatment of the retina, in particular the retinal pigment epithelium (RPE), may be able to slow down or prevent AMD progression. This is believed to be achieved primarily by improving the functional capacity of the RPE. Laser treatment is purported to improve RPE phagocytosis in particular, as a result of which drusen and pigment changes are broken down and the functional capacity of the entire retina is improved. Furthermore, paracrine effects have been postulated due to the expression of, e.g., matrix metalloproteinases, which are found in the entire retina and lead to a reduction in drusen and a structural stabilization of Bruch's membrane [2, 3]. In more detail, conventional laser therapy

Published online: 17 April 2019

using green-wavelength lasers results in 50%–60% of the laser energy being absorbed by the melanosomes in the RPE. This causes thermal destruction of the RPE as well as thermal coagulation of the overlying neurosensory retina [4]. The biological reaction following laser application does not require the coagulation and destruction of the photoreceptors themselves—the goal is merely the laser-induced migration and proliferation of the RPE cells adjacent to the laser defect, which are able to cover this defect within a number of days [5–7]. It is possible that precisely this defect coverage achieves the above-mentioned increase in RPE function. This would probably promote drusen regression in intermediate AMD. Framme et al. [8] provide an overview of the basic principles of retinal laser therapy.

Laser coagulation of drusen

Drusen represent the main risk factor for the development of choroidal neovascularization (CNV). The risk of developing CNV within 5 years in the case of large soft drusen with focal hyperpigmentation is between 58 and 73% [9]. It is for this reason that methods are being sought to reduce the risk of CVN. It was observed early on that drusen disappear following laser coagulation—and not only in treated areas, but also in untreated areas [10, 11]. However, the degradation and regression of drusen is also seen in the natural course of the disease. A number of mostly small studies have investigated whether "drusen coagulation" leads not only to drusen reduction in general, but whether it can also significantly contribute to CNV prevention. However, patient numbers in the individual studies were low and ranged from $n = 12$ to $n = 46$. The inclusion criteria were heterogeneous and patients were mostly treated with laser light in the green-wavelength spectrum with 50-µm to 200-µm large burns of varying intensity and number ($n = 12$ to $n = 200$). The observation period was between 1 and 3 years [9–14]. The results were likewise highly heterogeneous, with drusen disappearance rates ranging from 52% [11] to 100% [13, 14] of the total drusen area in the macular region. An extremely low CNV rate was mostly seen in the treatment group: as low as 0/30 and 1/17 in two studies over 3 years [9, 15]. On the other hand, the CNV rate in two other studies was 7% and 8% [12, 14]. In some cases, the rate was higher than in non-treated eyes.

The results of a large-scale prospective comparative study conducted by the Choroidal Neovascularization Prevention Trial Research Group (CNPTRG) in 1998 contributed to a fundamental review of the concept [16, 17]. The study eye was primarily treated in a one-off approach with 20 visible laser burns (100 µm, 100 ms) in three rows in the temporal perifoveal region. Drusen were not directly treated and follow-up treatment was planned in the case that drusen reduction reached less than 50% at 6 months. Two patient collectives were investigated: 1. Fellow Eye Study Group ($n = 120$; 1st eye exudative, 2nd eye >10 drusen); 2. Bilateral Drusen Study Group ($n = 156$). In summary, the results revealed a > 90% reduction in drusen in the treatment group at 12 months and <10% in the control group. CNV development in the "fellow eye group" was $n = 10$ in the treatment group vs. $n = 2$ in the observation group and $n = 4$ vs. $n = 2$ in the "bilateral eye group" to the disadvantage of the treated eye. CNV was generally associated with the treatment area. Since the vast majority of CNV membranes were occult (16/18), the results were intensively discussed in view of the fact that that one would expect classic CNV membranes in the case of laser-induced defects in Bruch's membrane and RPE, whereas occult CNV membranes are more consistent with the nature of AMD. In addition, the laser burns—in contrast to the smaller studies cited here—were rigidly set (visibly gray-white), which could certainly be conducive to CNV genesis in patients with drusen maculopathy. Irrespective of these discussions, the study results put an end to conventional drusen coagulation for obvious reasons.

Some of the studies presented here, as well other studies published in the ensuing years, were evaluated in a systematic meta-analysis by the Cochrane collaboration in 2015. Overall, this analysis with the highest grade of evidence was *not* able to identify any effect of conventional laser therapy on the progression of AMD [18]. Although, as described above, drusen reduction was seen, this had no positive effect on disease progression, and late AMD (both geographic atrophy and CNV) and visual loss occurred just as often as in the untreated comparison group [18]. In some studies, the risk for CNV development in the area of laser scars—as discussed in relation to the CNPT study (see above)—was increased. No micropulse laser studies were evaluated in the Cochrane analysis, although one study with an 810-nm infrared laser was able to distinguish between visible and "invisible" burns (by halving pulse duration from 200 to 100 ms at the ophthalmoscopically visible power threshold) [19]. Interestingly, visual acuity improved significantly in this study irrespective of whether laser burns were visible or not ($p < 0.001$) [19]. Thus—assuming the CNV rate is not higher following laser treatment—it is quite possible that improved visual acuity or reduced metamorphopsia could also represent a positive criterion for laser treatment. However, based on this meta-analysis, it is currently not possible to recommend purely conventional laser therapy for the treatment of any stage of early, intermediate, or late AMD.

A novel approach: micropulse/subthreshold laser therapy

Micropulse or subthreshold laser therapy "without scar formation" could represent an alternative, given that, as described above, there is no evidence that conventional laser treatment confers a benefit. Even in the medium term, coagulation always causes RPE atrophy and retinal scars [20], which can actually increase in size over time (atrophic creep) [21], thereby leading to a significant deterioration in visual acuity even much later. There is no generally accepted definition for either term as yet, but rather they encompass a number of different procedures that are relatively difficult to differentiate and, as such, require explanation:

In contrast to conventional photocoagulation, subthreshold laser treatment

attempts to contain structural retinal damage in both the horizontal and, in particular, the vertical plane. The technique uses short-pulsed laser systems that minimize thermal damage beyond the target tissue, thereby leaving retinal tissue intact. However, in order to perform the treatment in such a way that ideally, the entire neurosensory layer in the region of the laser burn stays intact, extremely short laser pulses in the submicrosecond or even nanosecond range are required, which can only be achieved with special types of lasers.

With the method referred to as selective retina therapy (SRT), the repetitively applied 1.7-µs green laser pulses are so short (below the thermal relaxation time of the RPE) that heat develops only in the region of the RPE, meaning that photoreceptors are ideally no longer subject to thermal destruction. The formation of cavitation bubbles around melanosomes causes mechanical destruction of the RPE cell and heat development that takes place almost exclusively in the area of the melanosomes, and thus within the RPE cell [22]. Brinkmann et al. provide a detailed overview of this technique [23]. This method has demonstrated, both clinically and histologically, that the desired damage can be restricted to the primarily absorbing RPE and that the photoreceptor layer remains intact [24–26]. Laser systems that work with significantly longer pulse durations are not able to achieve this selective effect in a reproducible manner, since coagulation and photoreceptor damage can occur from a pulse length of as little as 5 µs, and always occurs above a pulse length of 50 µs, even if the laser burn is not ophthalmoscopically visible [27].

The micropulse lasers that have been on the market for some time emit micropulses up to at least 50 µs and generally work with 100-µs pulses or higher [28], and thus—one can assume—regularly induce thermal damage and cannot work selectively in terms of absolute photoreceptor preservation. Naturally this is only true if the applied laser energy—dependent on the power—is high enough for coagulation to occur. If the laser energy applied is too low, it is possible that only tissue heating without structural damage occurs. The therapeutic window between coagulation and potential simple heating of the RPE cells is extremely small with the laser parameters usually used (e.g., in diabetic macular edema), such as 100-µm spot size, 200-ms laser pulse duration at 5% duty cycle, and laser powers from 250 mW (yellow) to 750 mW (infrared) [29], and, at times, highly heterogeneous RPE pigmentation. In addition to use in the green wavelength range, this also applies in principle to systems in the yellow and infrared ranges, since, here again, maximum tissue heating occurs in the RPE due to absorption and heating maxima in RPE and neurosensory retina are roughly comparable [30]. This means that, with a certain degree of likelihood, it is quite possible that treatment using these laser parameters leads merely to heating of the RPE cells or—depending on whether the individual damage threshold is reached—directly to conventional photocoagulation. This cannot be controlled by the laser operator. The value of laser-induced RPE heating is currently not clear; however, what is known is that in vitro hyperthermia can alter RPE functionality, protect against oxidative stress, and prevent secretion of vascular endothelial growth factor (VEGF) [31]. Therefore, one can assume that, whatever the case, the laser—irrespective of whether through coagulation or merely through heating—may lead to some form of "treatment effect" (e.g., resolution of diabetic macular edema or drusen regression).

In contrast to SRT with 200-µm spots, 2RT treatment (Ellex Medical Lasers Ltd., Adelaide, Australia) works with large 400-µm spots and extremely short pulse times of only 3–4 ns. The pulses are so short that they might have greater potential to mechanically disrupt Bruch's membrane, which could lead to microhemorrhage. However, due to the system's special technology, this can evidently be well minimized and controlled. In contrast to the SRT technique, which selectively and uniformly destroys the RPE over the entire laser spot, the 2RT technique uses speckle formation in the laser profile. As a result, the entire laser spot consists of a random grid of small laser spots, so to speak. The laser energy applied over the entire spot is kept so low that no definitive RPE damage is caused and only small high-energy laser peaks (speckles) within this area induce very closely localized selective RPE damage. In the case of repetitive pulses, these effects occur incidentally at different sites within the spot, meaning that "treatment" has taken place at multiple sites over the entire area. A detailed description of this interesting technique can be found in the US patent "Retinal rejuvenation laser, Patent US 8496649 B2." The SRT technique, on the other hand, uses constant, reproducible, selective laser power over the entire spot profile. In principle, the technically selective effect on tissue of these two methods, irrespective of pulse duration in the lower micro- or nanosecond range, may be deemed similar in terms of the biological reaction.

Evidence on subthreshold treatment of drusen

With new and more selective laser treatments which do not cause scarring of the neurosensory retina (SRT and 2RT), laser treatment of drusen to reduce AMD progression should be revisited. As already described above, this photoreceptor-preserving effect cannot be achieved by reducing laser power in classic laser coagulation to such an extent that the laser burn remains ophthalmologically invisible. However, this procedure generally still results in classic coagulation and subsequent tissue scarring. Nevertheless, as described in Olk et al. [19], this principle was still investigated in further studies with an infrared laser (810 nm). Laser power at a 200-ms pulse duration was increased until a mild change in color could be seen ophthalmologically, at which point pulse duration was reduced to 100 ms and the treatment performed [32, 33]. As mentioned above, these are not micropulse laser treatments and should not be mistaken for such in this context; it was merely that by reducing pulse duration, half of the laser power was applied. Interestingly, the study conducted by Scorolli et al. [33] in 144 patients with bilateral soft drusen achieved an improvement in visual acuity in the

treated eyes, whereas visual acuity remained unchanged in the study by Rodanant et al. [32] ($n = 100$). A large prospective randomized PTAMD (prophylactic treatment of age-related macular degeneration) study investigated the subthreshold technique in two arms in unilaterally (1st eye already exudative) and bilaterally suitable patients [34, 35]. A grid of 48 lesions 125 µm in size at a distance of 0.5–2.0 disc size from the center was applied. In the unilaterally suitable patients ($n = 240$), a significantly increased CNV rate was seen over 2 years in the treated eyes (15.8%) vs. untreated eyes (1.4%; $p = 0.05$) [35]. There was no difference in the CNV rate in the bilateral group ($n = 1278$ eyes) between treated and untreated eyes. However, there was a moderate improvement in visual acuity at 2 years (1.5 letters difference, $p = 0.04$) [34]. The authors concluded that a single subthreshold infrared laser treatment confers *no* protection against the development of CNV. It may be interesting to note in this context that spectral domain optical coherence tomography (SD-OCT) examinations in these patients showed definitive damage to the outer retinal layers, underlining the fact that this technique does not appear to be sufficiently selective [36].

Initial pilot studies on a small number of patients demonstrated that drusen in 7 of 10 patients could be reduced using the SRT technique [37]. Treatment was carried out with a 527-nm Nd:YLF laser (laser parameters: 1.7-µs pulse duration; 100 and 500 pulses at a repetition rate of 500 Hz; spot size: 160 µm; laser power: 70–100 µJ). Another study with a Zeiss Nd:YAG prototype used similar treatment parameters and identified drusen reduction in 3/5 patients in whom visual acuity remained stable [38]. Both studies had the primary goal to clinically test this special novel technology (SRT), meaning that drusen patients represented only a proportion of the patients treated. Patients with diabetic macular edema or macular edema following vein occlusion were also treated. As such, the studies were not designed to demonstrate a definitive reduction in the CNV rate following drusen treatment. In 2009, SD-OCT also provided clinical evidence that SRT lesions are highly selective and do not cause detectable photoreceptor damage [39].

In contrast to diabetic macular edeme, for which a number of studies have assessed different commercially available micropulse laser systems, hardly any studies exist for the laser treatment of drusen in AMD using micropulse laser systems. As mentioned above, one can assume that pulses over 50 µs are not reproducibly selective, meaning that similar effects as seen with the subthreshold technique propagated by Friberg et al. [34, 35] with conventional continuous wave lasers could be expected, since both procedures produce classic coagulation effects. However, this can only be demonstrated clinically by a large prospective study with an appropriate follow-up period.

The Ellex® System (2RT, Ellex Medical Lasers Ltd.) already described above, with 3- to 4-ns laser pulses, is marketed under the term "rejuvenation." This technique does indeed enable selective RPE effects. A small pilot study tested this laser therapy in 50 patients (on one eye) with intermediate AMD. None of the treated eyes had developed CNV at either 12 or 24 months; however, central atrophy occurred in two treated eyes. A drusen reduction of 44% in treated eyes vs. 22% in the untreated fellow eye was achieved, as well as a moderate functional improvement in flicker perimetry [2, 40]. There were no safety concerns in this pilot study with regard to the use of a nanosecond laser in the region of the central retina outside the central fovea. However, there was no control group and no randomization.

A large clinical trial with this nanosecond laser (2RT, Ellex Medical Lasers Ltd.) is currently underway (Laser Intervention in Early Age-Related Macular Degeneration Study, LEAD), but has not yet been completed and, as such, no results are available (Clinical Trials Identifier NCT01790802; clinicaltrials.gov). Results are expected in June 2018. This multicenter double-blind randomized trial over a 3-year period was started in 2011 and included 292 patients. Patients were treated with 12 laser spots superiorly and inferiorly just inside of the large vascular arcades. The results of this study will yield the first valid data describing the effect of micro-/nanopulse laser treatment on drusen in AMD in a randomized design. If these demonstrate an advantage for selective laser treatment, this would represent the first scientifically proven evidence of a benefit for the treatment of early and/or intermediate AMD using surgical laser techniques.

Conclusion

The terms subthreshold and micropulse/nanopulse laser treatment as therapeutic options are not defined precisely enough, particularly with regard to their therapeutic effect at the RPE level, while at the same time preserving the photoreceptors. As discussed, this is technically possible using SRT and 2RT and represents an undisputed advantage in macular laser treatment.

The subthreshold techniques used in the field of drusen treatment represented no more than purely classic continuous wave laser treatments with reduced pulse durations. Here, despite clinically invisible laser lesions on the cellular level, the same coagulation and tissue destruction can still occur. This also applies in general to micropulse lasers with minimal pulse durations of only 50 µs and higher, even though coagulation damage here may at least be locally restricted to a horizontal direction. There are no results as yet for drusen coagulation from randomized studies using techniques such as SRT and 2RT. None of the results from studies using conventional lasers discussed here have been able to yield sufficient evidence that laser treatment of drusen, despite drusen reduction, achieves the primary target, i.e., to reduce the CNV rate.

Given the lack of evidence for its efficacy—not least in the meta-analysis conducted by the Cochrane collaboration—conventional laser therapy should not be used to treat early, intermediate, or late AMD [18]. The same applies at present to micro-/nanopulse techniques, for which there are likewise insufficient evidence-based data to support a positive treatment effect on the course of AMD. Therefore, at this stage, treatment

should only be performed in the context of controlled prospective clinical trials that have been registered with the appropriate regulatory bodies. If relevant micropulse studies additionally demonstrate, e.g., improved visual function or a reduction in metamorphopsia, in the future (and as long as the CNV rate remains at least stable), specialized treatment of this kind would be welcomed. For the time being, however, and in the continuing absence of evidence-based data, laser treatment of drusen should not take place outside clinical trials nor without making appropriate reference to the limited evidence.

Supplementary statement of the BVA, DOG, and RG on laser treatment of drusen in age-related macular degeneration (AMD)—October 2018

Key messages

- **Although conventional laser coagulation of drusen in age-related macular degeneration (AMD) results in their regression, it does not, according to current knowledge, reduce the risk of AMD progression and should therefore not be performed.**
- **Newer "micropulse" and/or "subthreshold laser techniques" are still undergoing clinical trials for early and intermediate dry AMD (in the absence of geographic atrophy). There is currently insufficient scientific evidence to conclusively assess the efficacy or potential negative effects of these techniques in AMD.**
- **At present, no form of retinal laser treatment for dry AMD should be performed outside of clinical trials. Registration in a registry does not meet clinical trial requirements and is therefore insufficient.**

The above-mentioned key messages were formulated in a previous statement on this topic and the background and evidence can be found in the full-text version [41].

Although the following supplement presents new aspects, these do not result in any modifications to the key messages:

Since the publication of the statement, a randomized clinical trial has been conducted and published on a newer laser method in intermediate AMD, making a supplement to the 2017 statement necessary [42]. This study tested a nanosecond laser (2RT, Ellex Medical Lasers Ltd., Adelaide, Australia) in patients with bilateral intermediate AMD on one study eye each (Laser Intervention in Early Age-Related Macular Degeneration Study, LEAD; Clinical Trials Identifier NCT01790802; clinicaltrials.gov). Participants were either treated (treatment arm) or observed only (control arm) and followed-up over 3 years. In the treatment arm, a total of not more than 15 laser burns were applied (test burns and 12 treatment burns) to the edge of the macula (along the vascular arcades) every 6 months. The selection of study participants was based not only on morphological criteria (drusen size ≥125 µm in both eyes, no sign of very early late-stage atrophic AMD, i.e, nascent geographic atrophy), but also on functional criteria. Patients needed to be able to identify at least 69 letters in eye testing, corresponding to a decimal visual acuity of 0.5.

Overall, the LEAD trial did not achieve its goal (i.e., the primary endpoint) of slowing down progression to late AMD.

A number of points in the LEAD trial and how they were dealt with warrant critical scrutiny:

1. Treatment protocol
   No preliminary tests on the treatment protocol were carried out, as is necessary and usual, e.g., with dose-finding studies in drug testing. The treatment protocol was specified by the study investigators and then applied every 6 months. Both the localization of laser burns (along the vascular arcades, six on the upper and six on the lower arcades) and their frequency (every 6 months, i.e., six times in total during the LEAD study) warrant critical scrutiny. Localization and number were used in a small uncontrolled pilot study, and it was shown that this treatment protocol was safe [43, 44]. However, testing was not performed to establish whether fewer burns are sufficient or whether more burns, if appropriate, are more effective. Localization was also specified and not tested, as with repeat treatments, for which there is no evidence as yet.
2. Endpoint determination:
   The LEAD study evaluated late neovascular as well as atrophic AMD as endpoints. All previous laser studies primarily investigated the development of choroidal neovascularization (CNV). With regard to CNV development, this was equally as frequent in the treatment group as in the control group (7/119 laser vs. 5/124 sham).
3. Subgroup analyses:
   Unplanned subgroup analyses showed that treated subjects with only conventional drusen (i.e., drusen under the retinal pigment epithelium) exhibited a reduced rate of progression to late AMD (primarily early geographic atrophy, referred to here as nascent geographic atrophy). However, it was also shown that treated subjects with reticular pseudodrusen (in addition to conventional drusen) experienced a significantly higher rate of progression to late AMD. Therefore, patient selection for laser therapy is evidently of considerable importance. It is unclear to date whether and, if so, how many reticular pseudodrusen can be present when laser treatment is performed without damage being caused. It is also unclear what happens if reticular pseudodrusen occur following laser treatment with a nanosecond laser.
4. Side effects of nanosecond laser treatment:
   Retinal hemorrhage in the region of the laser burn occurred in 10 patients (6.8%) in total in the treatment group. This resolved without further complications such as secondary CNV. It is not yet clear whether the short laser pulse of the nanosecond laser increased the risk of bleeding. In the case of uncertainty as to

whether laser treatment is associated with an increased risk of bleeding, central lasering with a nanosecond laser in the macular region is not recommended.

The principal investigator of the LEAD study, Professor Robyn Guymer, explicitly stated in the LEAD study publication that further larger studies will be needed before the efficacy of the tested laser treatment could be assessed with certainty [42]. It is also important to ensure that no patients with, e.g., reticular pseudodrusen incur damage due to the laser treatment. The results of the LEAD study cannot be extrapolated to other types of lasers or methods.

Against this backdrop, the key messages as well as the 2017 statement remain valid in their entirety [41]. Further larger controlled clinical studies will be needed to assess the medium- and long-term efficacy of the nanosecond laser in intermediate AMD. Since efficacy was not investigated in any other form of early AMD in the LEAD study, no assessment can be made in this regard. Due to a lack of studies, efficacy can also not be assessed in late dry AMD (atrophic AMD or geographic atrophy). Registering cases in a treatment registry is not equivalent to—nor does is substitute—a clinical study.

Corresponding address

German Society of Ophthalmology (Deutsche Ophthalmologische Gesellschaft, DOG)
German Society of Ophthalmology (Deutsche Ophthalmologische Gesellschaft)
Platenstr. 1, 80336 Munich, Germany
geschaeftsstelle@dog.org

Compliance with ethical guidelines

Conflict of interest See Table 1 in the Appendix.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

The supplement containing this article is not sponsored by industry.

Table 1 Information on conflicts of interest[15]

	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 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 medicaments/ 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 (e.g., 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 institute, or an insurance company**
Bertram, Prof. Dr. med. Bernd	No	No	No	No	No	No	Yes *Berufsverband der Augenärzte* (BVA), *Deutsche Ophthalmologische Gesellschaft* (DOG), *Retinologische Gesellschaft*	No	Freelance ophthalmologist	No
Finger, Prof. Dr. med. Robert	Yes Opthea, Retina Implant, Santen, Novartis, Bayer, Santhera, Alimera	Yes Bayer, Ellex	Yes Novartis	No	No	No	Yes *Deutsche Ophthalmologische Gesellschaft* (DOG)	No	University Hospital Bonn	No
Framme, Prof. Dr. med. Carsten	Yes Bayer, Zeiss; in Advisory Boards for Novartis and Allergan	Yes Novartis, Bayer, Allergan, Zeiss, Heidelberg Engineering, Medupdate	Yes Novartis	No	No	No	Yes *Berufsverband der Augenärzte* (BVA), *Deutsche Ophthalmologische Gesellschaft* (DOG)	No	Hannover Medical School	No

Table 1 (Continued)

	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 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 medicaments/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 (e.g., 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 institute, or an insurance company**
Hoerauf, Prof. Dr. med. Hans	Yes Bayer, Alimera, Alcon/Npvartos, Thrombogenics, Allergan	Yes Bayer, Heidelberg Engineering, Alimera, Alcon/Novartis, TheaPharma, Thrombogenics, Allregan	Yes Bayer, Heidelberg Engineering, Carl Zeiss Meditec, Roche/Genentech, Ophthotech, Lutronic, Regeneron, Boehringer	No	Yes Shares: BASF, Bayer, Amgen, 3M, Johnson&Johnson, Roche, Siemens, Medtronic, Novartis, Merck, Glaxo Smith Kline	No	Yes Member of the Executive Committee of the *Deutsche Ophthalmologische Gesellschaft* (DOG), member of the executive board of the *Berufsverband der Augenärzte* (BVA)	No	Universitätsmedizin Göttingen	No
Holz, Prof. Dr. med. Frank G.	Yes Acucela, Allergan, Apellis, Bayer, Genentech/Roche, Geuder Graybug, Heidelberg Engineering, Lin BioScience, Novartis, Pixium Vision, Zeiss	Yes Acucela, Allergan, Apellis, Bayer, Formycon, Genentech/Roche, Geuder Graybug, Heidelberg Engineering, Lin BioScience, NightStar, Novartis, Zeiss	Yes Acucela, Allergan, Bayer, Centervue, Genentech/Roche, Heidelberg Engineering, Optos, Zeiss	No	No	No	Yes *Deutsche Ophthalmologische Gesellschaft* (DOG), *Berufsverband der Augenärzte* (BVA), EURETINA, *Retinologische Gesellschaft*	No	University Hospital Bonn	No

Table 1 (Continued)

	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 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 medicaments/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 (e.g., 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 institute, or an insurance company**
Pauleikhoff, Prof. Dr. med. Daniel	Yes Novartis, Bayer, Heidelberg Engineering	No	Yes Novartis, Bayer	No	No	No	Yes *Berufsverband der Augenärzte* (BVA), *Deutsche Ophthalmologische Gesellschaft* (DOG), *Retinologische Gesellschaft*	No	Self-employed	No

References

1. Lim LS, Mitchell P, Seddon JM et al (2012) Age-related macular degeneration. Lancet 379(9827):1728–1738. https://doi.org/10.1016/S0140-6736(12)60282-7
2. Jobling AI, Guymer RH, Vessey KA et al (2015) Nanosecond laser therapy reverses pathologic and molecular changes in age-related macular degeneration without retinal damage. FASEB J 29(2):696–710. https://doi.org/10.1096/fj.14-262444
3. Treumer F, Klettner A, Baltz J et al (2012) Vectorial release of matrix metalloproteinases (MMPs) from porcine RPE-choroid explants following selective retina therapy (SRT): towards slowing the macular ageing process. Exp Eye Res 97(1):63–72. https://doi.org/10.1016/j.exer.2012.02.011
4. Marshall J, Mellerio J (1967) Pathological development of retinal laser photocoagulations. Exp Eye Res 6(4):303–308. https://doi.org/10.1016/S0014-4835(67)80002-2
5. Del Priore LV, Glaser BM, Quigley HA et al (1989) Response of pig retinal pigment epithelium to laser photocoagulation in organ culture. Arch Ophthalmol 107(1):119–122. https://doi.org/10.1001/archopht.1989.01070010121039
6. Framme C, Kobuch K, Eckert E et al (2002) RPE in perfusion tissue culture and its response to laser application. Preliminary report. Ophthalmologica 216(5):320–328. https://doi.org/10.1159/000066184
7. Wallow IH (1984) Repair of the pigment epithelial barrier following photocoagulation. Arch Ophthalmol 102(1):126–135. https://doi.org/10.1001/archopht.1984.01040030104047
8. Framme C, Roider J, Brinkmann R et al (2008) Basic principles and clinical application of retinal laser therapy. Klin Monbl Augenheilkd 225(4):259–268. https://doi.org/10.1055/s-2008-1027202
9. Frennesson C, Nilsson SE (1998) Prophylactic laser treatment in early age related maculopathy reduced the incidence of exudative complications. Br J Ophthalmol 82:1169–1174
10. Sigelman J (1991) Foveal drusen resorption one year after perifoveal laser photocoagulation. Ophthalmology 98(9):1379–1383. https://doi.org/10.1016/S0161-6420(91)32122-5
11. Wetzig PC (1988) Treatment of drusen-related aging macular degeneration by photocoagulation. Trans Am Ophthalmol Soc 86:276–290
12. Guymer RH, Gross-Jendroska M, Owens SL et al (1997) Laser treatment in subjects with high-risk clinical features of age-related macular degeneration. Posterior pole appearance and retinal function. Arch Ophthalmol 115(5):595–603. https://doi.org/10.1001/archopht.1997.01100150597004
13. Little HL, Showman JM, Brown BW (1997) A pilot randomized controlled study on the effect of laser photocoagulation of confluent soft macular drusen. Ophthalmology 104(4):623–631. https://doi.org/10.1016/S0161-6420(97)30261-9
14. Sarks SH, Arnold JJ, Sarks JP et al (1996) Prophylactic perifoveal laser treatment of soft drusen. Aust N Z J Ophthalmol 24(1):15–26. https://doi.org/10.1111/j.1442-9071.1996.tb01546.x
15. Figueroa MS, Regueras A, Bertrand J et al (1997) Laser photocoagulation for macular soft drusen. Updated results. Retina 17(5):378–384
16. The Choroidal Neovascularization Prevention Trial Research Group (1998) Choroidal neovascularization in the Choroidal Neovascularization Pre-

vention Trial. Ophthalmology 105(8):1364–1372. https://doi.org/10.1016/S0161-6420(98)98014-9
17. Choroidal Neovascularization Prevention Trial Research Group. (1998) Laser treatment in eyes with large drusen. Short-term effects seen in a pilot randomized clinical trial. Ophthalmology 105(1):11–23
18. Virgili G, Michelessi M, Parodi MB et al (2015) Laser treatment of drusen to prevent progression to advanced age-related macular degeneration. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD006537.pub3
19. Olk RJ, Friberg TR, Stickney KL et al (1999) Therapeutic benefits of infrared (810-nm) diode laser macular grid photocoagulation in prophylactic treatment of nonexudative age-related macular degeneration: two-year results of a randomized pilot study. Ophthalmology 106(11):2082–2090. https://doi.org/10.1016/S0161-6420(99)90487-6
20. Framme C, Roider J (2004) Immediate and long-term changes of fundus autofluorescence in continuous wave laser lesions of the retina. Ophthalmic Surg Lasers Imaging 35(2):131–138
21. Morgan CM, Schatz H (1989) Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. Ophthalmology 96(1):96–103. https://doi.org/10.1016/S0161-6420(89)32924-1
22. Lee H, Alt C, Pitsillides CM et al (2007) Optical detection of intracellular cavitation during selective laser targeting of the retinal pigment epithelium: dependence of cell death mechanism on pulse duration. J Biomed Opt 12(6):64034. https://doi.org/10.1117/1.2804078
23. Brinkmann R, Schule G, Neumann J et al (2006) Selective retina therapy: methods, technique, and online dosimetry. Ophthalmologe 103(10):839–849. https://doi.org/10.1007/s00347-006-1416-6
24. Framme C, Schuele G, Roider J et al (2004) Influence of pulse duration and pulse number in selective RPE laser treatment. Lasers Surg Med 34(3):206–215. https://doi.org/10.1002/lsm.20022
25. Roider J, Hillenkamp F, Flotte T et al (1993) Microphotocoagulation: selective effects of repetitive short laser pulses. Proc Natl Acad Sci Usa 90(18):8643–8647
26. Roider J, Michaud NA, Flotte TJ et al (1992) Response of the retinal pigment epithelium to selective photocoagulation. Arch Ophthalmol 110(12):1786–1792. https://doi.org/10.1001/archopht.1992.01080240126045
27. Schuele G, Rumohr M, Huettmann G et al (2005) RPE damage thresholds and mechanisms for laser exposure in the microsecond-to-millisecond time regimen. Invest Ophthalmol Vis Sci 46(2):714–719. https://doi.org/10.1167/iovs.04-0136
28. Dorin G (2003) Subthreshold and micropulse diode laser photocoagulation. Semin Ophthalmol 18(3):147–153. https://doi.org/10.1076/soph.18.3.147.29812
29. Vujosevic S, Martini F, Longhin E et al (2015) Subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser in center-involving diabetic macular edema: morphologic and functional safety. Retina 35(8):1594–1603. https://doi.org/10.1097/IAE.0000000000000521
30. Gabel VP, Birngruber R, Hillenkamp F (1978) Visible and near infrared light absorption in pigment epithelium and choroid. In: Shimizu K (ed) Visible and near infrared light absorption in pigment epithelium and choroid. Excerpta Medica, Kyoto, pp 658–662
31. Iwami H, Pruessner J, Shiraki K et al (2014) Protective effect of a laser-induced sub-lethal temperature rise on RPE cells from oxidative stress. Exp Eye Res 124:37–47. https://doi.org/10.1016/j.exer.2014.04.014
32. Rodanant N, Friberg TR, Cheng L et al (2002) Predictors of drusen reduction after subthreshold infrared (810 nm) diode laser macular grid photocoagulation for nonexudative age-related macular degeneration. Am J Ophthalmol 134(4):577–585. https://doi.org/10.1016/S0002-9394(02)01691-4
33. Scorolli L, Corazza D, Morara M et al (2003) Argon laser vs. subthreshold infrared (810-nm) diode laser macular grid photocoagulation in nonexudative age-related macular degeneration. Can J Ophthalmol 38(6):489–495. https://doi.org/10.1016/S0008-4182(03)80028-5
34. Friberg TR, Brennen PM, Freeman WR et al (2009) Prophylactic treatment of age-related macular degeneration report number 2: 810-nanometer laser to eyes with drusen: bilaterally eligible patients. Ophthalmic Surg Lasers Imaging 40(6):530–538. https://doi.org/10.3928/15428877-20091030-01
35. Friberg TR, Musch DC, Lim JI et al (2006) Prophylactic treatment of age-related macular degeneration report number 1: 810-nanometer laser to eyes with drusen. Unilaterally eligible patients. Ophthalmology 113(4):612–622e. https://doi.org/10.1016/j.ophtha.2005.10.066
36. Mojana F, Brar M, Cheng L et al (2011) Long-term SD-OCT/SLO imaging of neuroretina and retinal pigment epithelium after subthreshold infrared laser treatment of drusen. Retina 31(2):235–242. https://doi.org/10.1097/IAE.0b013e3181ec80ad
37. Roider J, Brinkmann R, Wirbelauer C et al (2000) Subthreshold (retinal pigment epithelium) photocoagulation in macular diseases: a pilot study. Br J Ophthalmol 84(1):40–47
38. Framme C, Brinkmann R, Birngruber R et al (2002) Autofluorescence imaging after selective RPE laser treatment in macular diseases and clinical outcome: a pilot study. Br J Ophthalmol 86(10):1099–1106
39. Framme C, Walter A, Prahs P et al (2009) Structural changes of the retina after conventional laser photocoagulation and selective retina treatment (SRT) in spectral domain OCT. Curr Eye Res 34(7):568–579. https://doi.org/10.1080/02713680902964892
40. Guymer RH, Brassington KH, Dimitrov P et al (2014) Nanosecond-laser application in intermediate AMD: 12-month results of fundus appearance and macular function. Clin Experiment Ophthalmol 42(5):466–479. https://doi.org/10.1111/ceo.12247
41. Berufsverband der Augenärzte Deutschlands e. V., Deutsche Ophthalmologische Gesellschaft, Retinologische Gesellschaft e. V. (2017) Stellungnahme des BVA, der DOG und der RG zur Lasertherapie von Drusen bei altersabhangiger Makuladegeneration (AMD) : Stand August 2017. Ophthalmologe 114:1008–1014
42. Guymer RH, Wu Z, Hodgson LA, Caruso E, Brassington KH et al (2018) Subthreshold nanosecond laser intervention in age-related macular degeneration: the LEAD randomized controlled clinical trial. Ophthalmology. https://doi.org/10.1016/j.oret.2016.12.001
43. Guymer RH, Brassington KH, Dimitrov P, Makeyeva G, Plunkett M et al (2014) Nanosecond-laser application in intermediate AMD: 12-month results of fundus appearance and macular function. Clin Exp Ophthalmol 42:466–479
44. Jobling AI, Guymer RH, Vessey KA, Greferath U, Mills SA et al (2015) Nanosecond laser therapy reverses pathologic and molecular changes in age-related macular degeneration without retinal damage. FASEB J 29:696–710