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MINI REVIEW

# Subthreshold laser treatment in retinal diseases: a mini review

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## Abstract

**Purpose** To summarize the mechanism and the clinical applications of subthreshold laser (STL) in retinal practice. Subthreshold or "non-destructive" laser includes all types of laser treatments that produce minimal or no damage to the tissues and no visible signs after application.

**Methods** A descriptive review of articles from literature databases (PubMed, Medline, Embase, Cochrane, Web of Science) published before August 2023, which discuss current STL treatments of retinal diseases.

**Results** This review provides evidence for STL as a treatment option for central serous chorioretinopathy, diabetic retinopathy, age-related macular degeneration, macular edema due to retinal vein occlusion, and other maculopathies. In most published reports, STL has shown a therapeutic effect without damage to the underlying tissue.

**Conclusion** Subthreshold laser treatment has shown safety and efficacy in the management of some retinal and macular diseases. Stimulation of the retinal pigment epithelium without destroying adjacent neuroretina has been shown to be sufficient in inducing retinal repair in many clinical cases. Recent research and clinical studies continue to explore the mechanisms and improving therapeutic benefits of this technology as well as extend the range of retinal disorders treatable by this modality.

**Keywords** Subthreshold retinal laser · Micropulse retinal laser · Selective retina therapy · Pattern laser photocoagulation · Nanosecond retina laser

**Key messages**

***What is known:***

- Subthreshold laser is a treatment approach, which achieves therapeutic effects without destruction of the retinal tissue.
- Based on the available studies its safety and efficacy have been proven for many retinal disorders.

***What is new:***

- Subthreshold micropulse laser combined with anti-VEGF intravitreal therapy can reduce the number of injections necessary to maintain therapeutic effect.
- Subthreshold micropulse laser has the potential to slowing the progression of geographic atrophy and delaying the neovascular conversion in age-related macular degeneration.

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## Introduction

Subthreshold laser treatment (STL) is a newly adopted treatment modality introduced for the treatment of retinal diseases. Up to date, clear recommendations for the use of STL in specific clinical entities have not been formulated; thus, its use is based on the results of published studies and surgeon's discretion. The aim of this review is to highlight the basics of the STL mode of action together with indications for its possible application in retinal diseases. For that purpose,

a thorough literature search of medical databases (PubMed, Medline, Embase, Cochrane, Web of Science) was performed using the following terms: subthreshold laser, subthreshold micropulse laser, end-point management; central serous chorioretinopathy, diabetic retinopathy, age-related macular degeneration, retinal vein occlusion, pseudophakic edema, and epiretinal membrane. The presentation of results of relevant publications was limited to trials involving a larger number of patients and followed the rules of descriptive mini-review outlined by the journal. The literature search included published reports through August 2023 predominantly published in English language.

## Basics of subthreshold laser use

Subthreshold or "non-destructive" laser (STL) includes all types of laser treatments that produce no or just minimal damage to the tissues with none or minor visible signs after application. These modalities include subthreshold micropulse laser (SML), pattern scanning laser (PASCAL) laser with EndPoint software, and selective retina therapy (SRT) with micro or nanosecond (2RT) laser. The first two forms of laser application are truly "non-damaging" as their idea is to treat retinal pigment epithelium (RPE) without eliciting any damage or visible trace at the retina. On the other hand, the principle of SRT and 2RT lasers is to selectively destroy a small number of the RPE cells and thus stimulate the growth of the new cells that are devoid of the flaws in function of the remaining old ones. Nevertheless, all the above-mentioned techniques achieve therapeutic effects without significant destruction of the retinal tissue, which is the feature of conventional continuous wave (CW) "suprathreshold" laser. The outcome of "suprathreshold" CW laser retinal photocoagulation is a full-thickness retinal scar, visible as a white laser spot at the retina [1, 2]. Theoretical and clinical research have proven that full-thickness retinal damage is not necessary to achieve the beneficial treatment effects [3]. Laboratory experiments have shown that the therapeutic effect in subthreshold treatments depends on laser-induced production of heat shock proteins (HSP), which is elicited with STL and not with higher, damaging energy settings [4]. The beneficial effect of HSP production and subsequent improvement of RPE function as a pump can elicit therapeutic effect in retinal diseases characterized by retinal edema or subretinal fluid accumulation, such as central serous chorioretinopathy (CSCR), diabetic macular edema (DME), or macular edema secondary to retinal vein occlusion (RVO).

In SML, a train of microsecond laser pulses "on" (100 to 300 µs) is separated by quiet "off" intervals (1700 to 1900 µs) which allows cooling of the tissue and prevents thermal damage. Such a form of laser energy delivery provides a selective treatment of the RPE and sparing of the neuroretina and the choroid. The ratio between "on" and total exposure time is called the duty cycle and can be adjusted for a specific clinical case to achieve expected effects. For the treatment of retinal disorders, the value of 5% is considered effective and safe [1, 2, 5]. It has been suggested that expression of HSPs by the RPE following SML provides reduction of the level of inflammatory cytokines and permeability factors and improves the blood-retinal barrier, but also modulates cell self-repair and optimizes its function [6]. "The reset to default" theory states that a burst of HSPs provides cell repair that restores its normal metabolism [7]. All these tissue-protective features of SML seem to result in better functional results compared with CW laser. For example, treatment with SML provides color vision and contrast sensitivity preservation which is not the attribute of conventional laser [8].

Pattern laser PASCAL provides the multispot option of laser treatment with a significantly shorter pulse duration. It can be used as a classic CW laser with a single impact duration 5 to 20 times shorter compared to a classic photocoagulator. Additional option of that device provides pattern laser spots with a pulse duration of 10 to 30 ms. Although the exposure time of a single pulse is at least 100 times longer compared to SML, the Endpoint Management (EpM) software uses a mathematic algorithm to modulate the power and duration of the laser to achieve a photothermal effect without retinal damage [1, 2]. Thus, the principle of EpM is similar to SML, however achieved with different laser settings.

In SRT and nanosecond 2RT laser, RPE cells located outside the retinal center are selectively targeted by microsecond or nanosecond laser, respectively, without affecting the photoreceptors or the choroid. Melanosomes of the RPE are exposed causing microbubble formation and selective RPE cell disruption. The healing process stimulates RPE cell migration and proliferation and improves the metabolism of RPE [2, 3]. The clinical outcome is usually assessed by change in best corrected visual acuity and structural changes on spectral-domain optical coherence tomography (Figs. 1, 2, 3, and 4); however, other parameters of vision should be assessed as well.

## STL in central serous chorioretinopathy treatment

Central serous chorioretinopathy is a common macular disorder believed to occur due to primary choroidal hyperpermeability and secondary RPE dysfunction which cause a serous retinal detachment. Before the onset of non-damaging laser therapies, 3–4 months of observation was recommended in expectation of spontaneous resolution of subretinal fluid (SRF) [9].

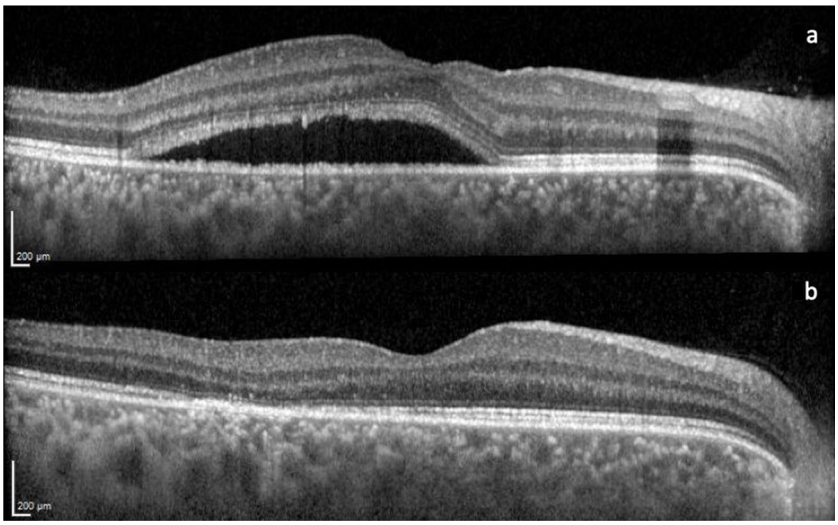


**Fig. 1** A 49-year-old male with best corrected visual acuity of 20/100 in his right eye. Spectral optical coherence tomography demonstrated subretinal fluid due to central serous chorioretinopathy of 4 months duration (**a**). Following subthreshold micropulse treatment, the foveal anatomy is restored (**b**) and visual acuity improves to 20/20

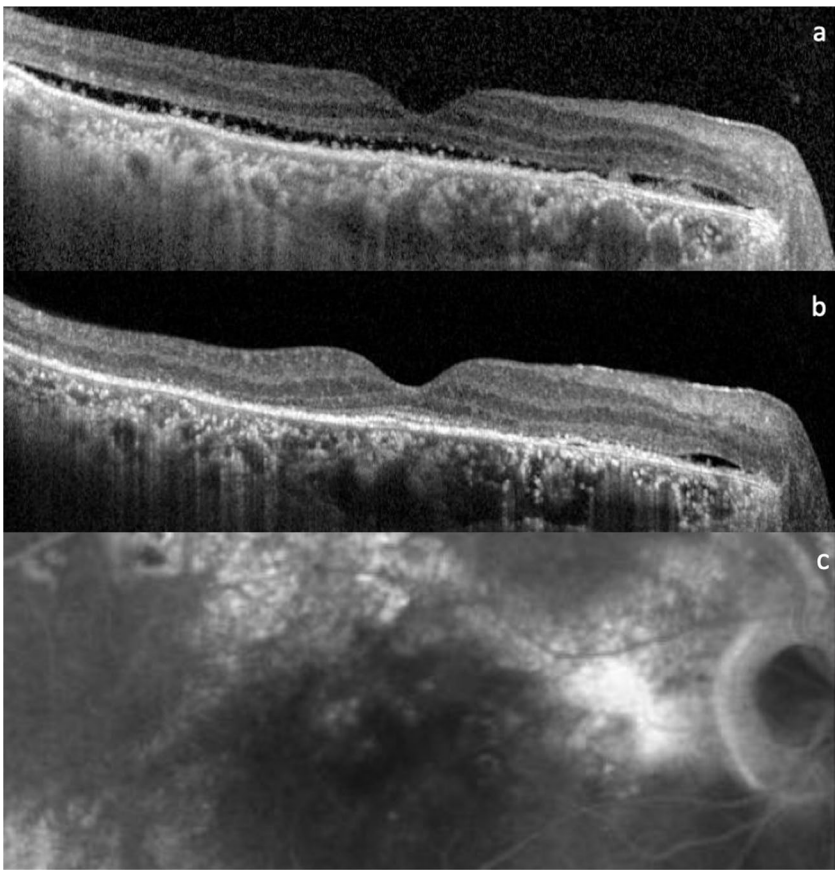


**Fig. 2** A 44-year-old male with chronic central serous chorioretinopathy of 6 years duration and best corrected visual acuity of 20/80. Spectral optical coherence tomography demonstrated diffuse subretinal fluid and thickened choroid (**a**). Following subthreshold micropulse treatment (**b**), the foveal anatomy is restored and visual acuity improves to 20/40. A follow-up at 9 months showed no disease recurrence. Pre-treatment fundus fluorescein angiogram demonstrates widespread defects in the retinal pigment epithelium (**c**). Those were the areas targeted with micropulse laser

Most of the studies on SML in chronic CSCR reported relatively high percentages of SRF resorption (40–80%) but only moderate vision improvement [5, 10–13]. Early initiation of treatment was reported to provide better functional results; thus, treatment without delay is advocated by some researchers [14]. Wavelengths of 577 and 810 nm are used for treatment of chronic CSCR in 3 strategies of laser application: area of leakage point, area of SRF presence based on optical coherence tomography (OCT), or panmacular treatment [15]. In case of a lack of response or worsening, the second session of SML could be performed at 6 weeks after the first treatment [5, 16]. One study found it to be superior to photodynamic therapy (PDT) in improving visual and anatomical outcomes at 6 months [17]. Most

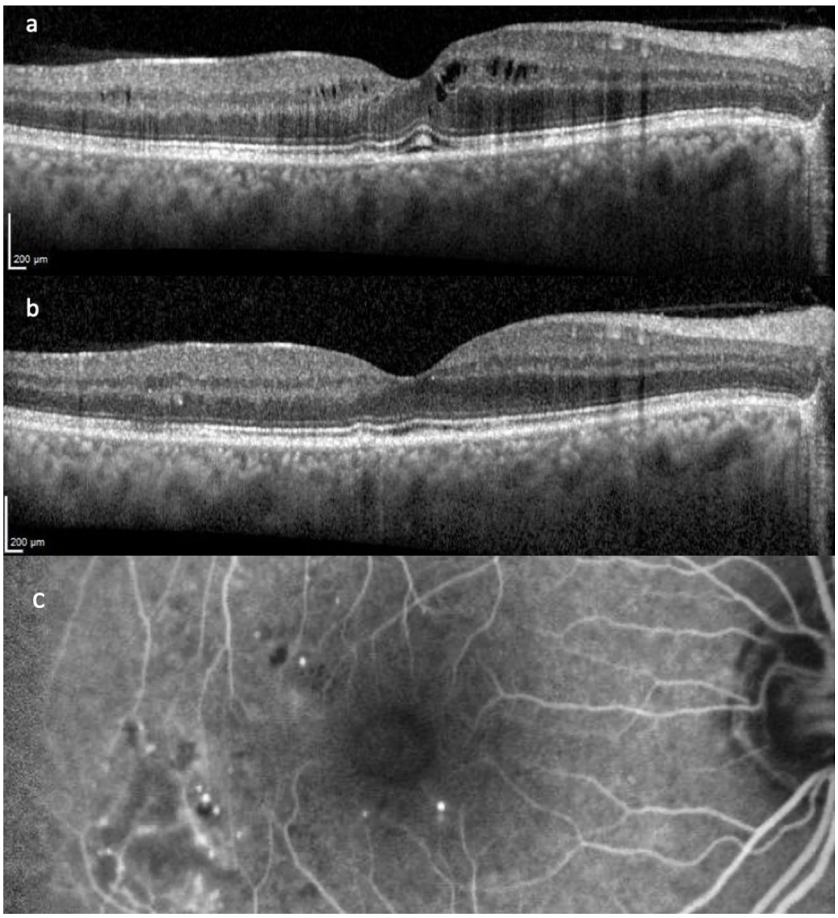


**Fig. 3** A 52-year-old female with moderate non-proliferative diabetic retinopathy presents with the best corrected visual acuity of 20/40. Spectral optical coherence tomography demonstrated diabetic macular edema (**a**). Following subthreshold micropulse treatment (**b**), the intraretinal fluid disappears and visual acuity improves to 20/25 at 6 months post-treatment. **c** Fundus fluorescein angiogram before treatment demonstrates diabetic microaneurysms and areas of extramacular capillary non-perfusion. Micropulse laser targeted areas of retinal pathology excluding the fovea

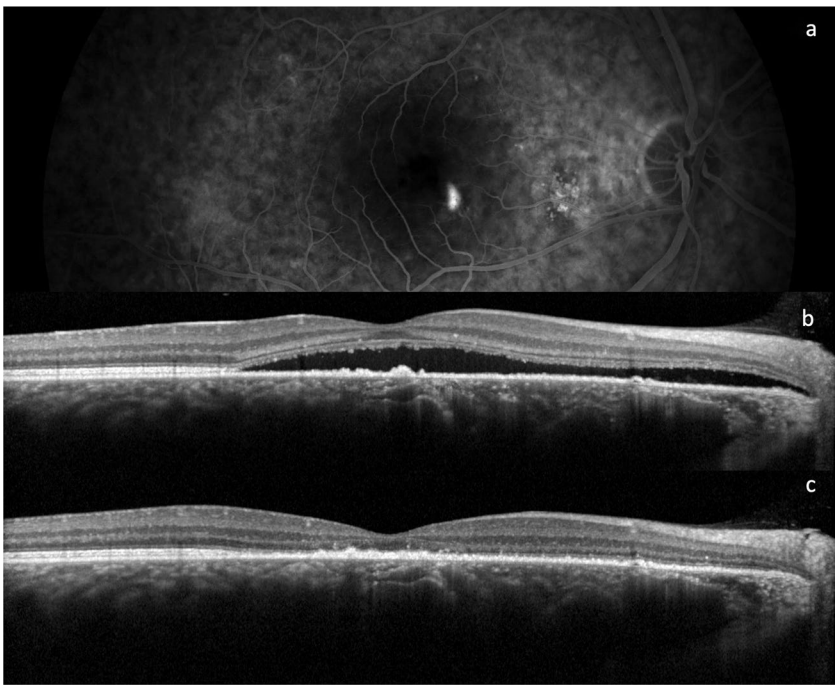


**Fig. 4** A 47-year-old patient with central serous chorioretinopathy shows smokestack leakage of fundus fluorescein angiogram (**a**). Pre-treatment spectral optical coherence tomography demonstrates subretinal fluid (**b**) and reduction of central retinal thickness by − 32 µm 3 months after panmacular subthreshold micropulse laser treatment (**c**)

of the published studies comparing PDT and SML in the treatment of chronic CSCR do not find statistically significant difference neither in morphological or functional outcome [18, 19]. The exception is a PLACE study according to which PDT appeared to be more effective in resolution of SRF but not quality of life improvement. When compared to PDT, SML is cheap, easily available, and does not involve the intravenous application of a photosensitive drug with potential systemic reactions. On the other hand, not all the patients respond to SML, especially the long-standing cases with compromised retinal morphology and significantly increased choroidal thickness [20]. PASCAL with EpM and SRT were also tried in the treatment of CSCR; however, available published reports are very scarce [21].

## STL in diabetic retinopathy (DR) treatment

Based on clinical trial evidence, there is significantly higher vision improvement in patients treated with anti-VEGF compared with conventional laser. However, conventional laser is still an option in non-center involved DME or as an additional treatment to anti-VEGF injections [22].

An increasing number of studies have confirmed the efficacy of SML in DME treatment [5, 23–25]. Scholz et al. have summarized the average improvement in the treatment of DME by SML in 613 patients from 11 studies [26]. The average best corrected visual acuity (BCVA) change was + 1.26 letters (range − 6.6 to 19), and the average central retinal thickness (CRT) reduction was 74.9 µm (range—48 to 138 µm to). The wide range of results indicates that there is a group of patients that has the potential to benefit more than average. European Society of Retina Specialists EURETINA states that STL can be helpful in the treatment of early diffuse DME with higher visual acuity [27]. It is worth mentioning that SML applied in DME not only optimizes the RPE function, but also improves retinal vascularity observed on OCT angiography [28]. In the study on 35 eyes treated with SML, Vujosevic et al. reported a decrease of the foveal avascular zone in the deep capillary plexus (DCP) at 6 months ($p = 0.01$). Additionally, the area of cysts decreased in the superficial capillary plexus (SCP) at 3 months and 6 months ($p = 0.038$; $p = 0.049$) and in DCP at 6 months ($p = 0.0071$). The number of microaneurysms decreased at 6 months in the SCP ($p = 0.0007$) and at 3 months and 6 months in DCP ($p = 0.048$; $p < 0.0001$) in SML-treated eyes. This therapy can be repeated as needed every 3 months. The most popular wavelengths used for SML treatment of DME are 577 nm and 810 nm in strategy based on the extent of macular edema or panmacular strategy [5]. In general, there is a preference for this treatment option in mild or moderate DME, with good BCVA and CRT ≤ 400 µm. Based on the studies, initial CRT is an important factor on the response to SML, as this laser is rarely effective in DME larger than 400 µm [1, 5, 29]. The efficacy of combination therapy: SML plus anti-VEGF in DME patients has shown that such combination allows to reduce the number of intravitreal injections with similar functional and morphological outcome [30].

Nanosecond laser (2RT) and SRT are applied very seldom in the treatment of DME; thus, it is difficult to draw solid conclusions on their efficacy. Improvement of BCVA after SRT was noted, however without morphological improvement [31].

## STL in age-related macular degeneration treatment

Classic laser photocoagulation was tried for the treatment of drusen in the dry form of AMD as early as in the seventies of the twentieth century [32]. Those studies were followed by subsequent research that reported drusen regression after CW laser treatment [33]. Nevertheless, later research proved an increased risk of development of choroidal neovascularization after application of traditional laser to drusen, and this treatment modality is currently not recommended for dry forms of AMD [34–36]. The discovery of anti-VEGF therapy and the better understanding of the laser-induced retinal damage led to the general abandonment of conventional CW laser for the treatment of exudative form of AMD [37]. Current research explores the new approaches focused on the treatment of dry AMD, including reduction of the number of drusen, improvement of BCVA, slowing progression of geographic atrophy (GA), or preventing the neovascular conversion. As it was suggested earlier, STL works by repair of the RPE metabolism, and dysfunction of the RPE and Bruch's membrane is believed to be the key factor in AMD pathogenesis [1]. In that light, STL has become a point of interest of researchers focused on the treatment of AMD.

Luttrull et al. reported a beneficial SML effect on the incidence of macular neovascularization (MNV) in eyes with high-risk dry AMD. The study included 547 eyes of 363 patients treated between 2008 and 2017 and MNV developed in 9 from 547 eyes (1.6%) [38]. The same author studied the effect of SML on GA progression in 67 eyes of 49 patients with GA. The rate of linear GA progression after panmacular SML slowed from an average annual rate of 137 to 73 µm per year (47% per year decline) with no adverse treatment effects [39]. On the other hand, Huang reported a poor effect of SML treatment of drusenoid pigment epithelium detachment (dPED). Twenty-one eyes were categorized in two groups based on the presence (6 eyes) or absence (15 eyes) of dPED collapse after SML treatment and followed up for a mean of 25.3 months. The outcome suggested that larger lesions are more likely to collapse after SML treatment [40].

The PASCAL laser study showed promising results in 20 patients with reticular pseudodrusen in AMD

patients treated with EpM. In the treated area, a significant decrease of the drusen stage and an increase in the outer nuclear layer thickness above the treated drusen was observed [41].

The use of SRT and nanosecond lasers in the prevention of advanced form of AMD was studied in the LEAD trial which evaluated the effect of the 2RT nanosecond laser compared to sham in intermediate AMD with large soft drusen. After 36 months, no benefit was found after 2RT in 292 treated eyes compared to sham controls with no overall delay in the rate of progression to late AMD (GA or MNV) [42]. On the other hand, post-hoc analysis showed in the group of eyes without coexistent reticular pseudodrusen that the progression was slowed without incidence of MNV. Subsequently, 2RT was recommended as a promising preventive treatment for specific forms of dry AMD with the need of further studies [43]. On the other hand, the use of SRT laser is associated also with the risks of disease progression, as documented in the study by Prahs et al. [44].

## Other retinal applications of STL

Primary treatment for cystoid macular edema (CME) associated with retinal vein occlusion includes intravitreal anti-VEGF or corticosteroid therapy. Eng and Leng have published a meta-analysis of 14 studies involving eyes diagnosed with branch RVO treated with SML. This therapy has proven to be as effective as conventional laser in reducing CME and improving BCVA without producing retinal scars, however not superior to intravitreal therapies. Combination treatment SML plus anti-VEGF resulted in a reduction of necessary intravitreal injections with similar functional effect as intravitreal monotherapy [45].

Besides large trials, there are available case series or case reports on STL application in other retinal disorders. Verdina published a report on SML application in 10 eyes with pseudophakic CME refractory to standard treatments (nonsteroidal anti-inflammatory eyedrops, topical steroids, oral indomethacin, sub-Tenon's triamcinolone injections and corticosteroid implants). After SML, a complete resolution of CME was observed in all eyes with statistically significant improvements in BCVA [46]. Minowa et al. applied EpM micropulse laser to 5 eyes of 5 patients with persistent serous retinal detachment due to tilted disc syndrome. Retinal detachment was completely absorbed in 4 eyes within 4 months after initial treatment [47]. An interesting application of SML was also assessed by Lutrull who applied a subthreshold micropulse laser on areas of retinal thickening and edema persistent after epiretinal membrane (ERM) peeling in 19 eyes. Both BCVA and macular thickness improved without any adverse events [48].

## What is the future for STL use?

The rise of drug therapy and the influence of the pharmaceutical industry have diverted professional attention and virtually all funding to drug-related clinical trials. In effect, retinal laser treatment is investigated only by small groups of researchers who are usually devoid of sufficient funding. The lack of trial funding for laser treatment has created the incorrect impression that retinal laser treatment has not progressed since a few decades and is thus no longer relevant in the drug era. This may be because retinal laser treatment does not produce revenue for the companies that sponsor over 95% of all clinical trials in medicine and ophthalmology, produce revenue for numerous practitioner investigators for recruiting and treating patients in the many large industry-funded clinical trials, and financially support all major ophthalmic journals and professional societies alike. Thus, data for retinal laser treatment for four decades rely on small clinical trials, retrospective studies, and real-world data studies that can be done at far lower cost than large RCTs. Laser treatment advances are often dismissed as lacking sufficient data and large RCTs, despite highly consistent results from numerous sources.

Despite such negligence, many studies show that retinal laser treatment continues to be indispensable. Ongoing research and clinical studies continue to discover the mechanisms and therapeutic benefits of STL technologies. Navigated SML system, for instance, will make this treatment more predictable, transparent, and reproducible with the possibility to precisely document treatment parameters. In conjunction with advanced imaging such as OCT angiography and adaptive optics, we expect new observations in the impact of STL on retinal structure and function.

## Conclusion

Based on the available studies, the safety and efficacy of STL have been shown for several retinal disorders. Indications and acceptance of STL treatment are increasing; however, more rigorous research and controlled clinical trials are crucial to explore the full potential of this approach.

### Declarations

**Competing interests** Authors declare no competing interests.

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