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Variability of thermal subthreshold retinal laser treatment plans

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To investigate the variability in subthreshold laser treatment plans for patients with diabetic macular edema or central serous chorioretinopathy. Diagnostic images from 20 patients were utilized, and 25 retina specialists generated subthreshold treatment plans along with a self-rated experience level. Evaluation comprised of i) Area Variability (AV): quantifies the consensus regarding the covered area and is the difference between the areas planned by 75% and 25% of the participants ii) mean Centroid Distance (CD): level of agreement on the localization of a treatment. Subgroup analysis investigated the impact of participants' experience levels, utilizing the Mann-Whitney-Wilcoxon test. The predominant plan style is a targeted treatment approach (92%) and avoidance of subfoveal region (89%). Mean CD is 71.0 ± 37.5 pixels (≈half disc diameter) and mean AV is 9.8%±8.9%. A slight difference is observed between the 50-75% areas, but a notable distinction exists between the 25-50% areas. Subgroup analysis revealed CD and AV value of 75.9 pixels and 24% in the lower experience level group as opposed to 55.9 pixels and 8.6% in the higher experience level group. There is significant variability in treatment planning which reduces with increased experience of retina specialists. While consensus is observed around focal points, differences in the surrounding extents persist.

Threshold retinal laser treatments were introduced over 30 years ago through the Early Treatment of Diabetic Retinopathy Studies (ETDRS) to address Diabetic Macular Edema (DME), effectively preventing vision loss in patients with diabetic retinopathy[1]. Despite the extensive documentation of threshold lasers, varying treatment plans have been observed. Van Dijk et al. investigated the concordance of treatment spot locations among experts, comparing optical coherence tomography (OCT)-based plans with biomicroscopy-based plans[2]. Results indicated only a 50% overlap within each expert, accompanied by significant variability in the number of laser spots applied for the same patient among the various experts[2]. Similarly, Kozak et al. noted substantial differences in spot counts when plans were based on OCT versus fluoresceine angiography (FA)[3]. While there had not been a study comparing if these spot number difference lead to different clinical outcomes, the comparison of different plan strategies such as the ETDRS grid with a mild macular grid approach demonstrated significantly different treatment outcomes[4], suggesting that distinct laser strategies may impact clinical results.

A newer approach to retinal laser treatments involves using thermal subthreshold retinal laser treatment for managing conditions like central serous chorioretinopathy (CSCR) and DME[5]. The initial concept involves breaking down a continuous wave laser into microsecond pulses, achieving a Duty Cycle below 20%[6]. This reduction in total applied energy still induces a thermal increase to stimulate retinal pigment-epithelial cells while avoiding structural damage to the cells[6]. Another thermal subthreshold laser, known as the endpoint management system (EPM), maintains a local thermal increase by reducing the pulse duration to a range between 5ms and 10ms, simultaneously lowering the power according to the Arrhenius integral with the attempt to remain below the damaging threshold[7].

Both strategies have been applied and demonstrated promise in treating DME as well as CSCR[8,9]. Despite their widespread application, a shortage of large-scale clinical trials exists to substantiate their clinical efficacy. Consequently, numerous small-scale studies with highly variable outcomes have been conducted, leading to low-grade evaluations in meta-analyses. Meta-analyses, such as Wu et al.'s comparison of the photodynamic therapy (PDT) and microsecond pulse subthreshold laser (MSPL) for CSCR[10], underscore the considerable variability in the benefits of micropulse subthreshold laser treatments. Multiple parameters, including laser characteristics and settings like duty cycle, spot size, and pulse duration vary significantly between studies, and hence may result in different energies applied to the retina[11]. Only a few publications address this issue by comparing two set of parameters, such as 5% vs. 10% Duty Cycle (DC)[12] or fixed vs. variable[13] parameters. In addition to the physical

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parameters itself, it also remains uncertain whether differences in plan strategies contribute as an additional factor for the variability. Despite thorough descriptions and analyses of threshold laser concepts, a notable gap exists defining principles for subthreshold laser use across all indications. To address this, the Subthreshold Ophthalmic Laser Society (SOLS) and the International Retinal Laser Society (LIGHT) were established to standardize the approach to MSPL treatment in terms of laser parameters, but also in terms of subthreshold laser plan. The LIGHT group advocates a panmacular treatment, covering the entire retina between vascular arcades with confluent laser spots in a single session to ensure comprehensive coverage and prevent undertreatment[14]. In contrast, SOLS recommends treating edematous areas, including subfoveal regions, with a confluent grid of laser spots without spacing, with optional focal treatment of microaneurysms[15]. However, the verbal descriptions of these treatment plans pose a risk of ambiguity and variable interpretation. SOLS guidelines lack a precise definition of the "edematous" area, leading to edema size variability of up to 50%[2,3]. Similarly, the LIGHT group's suggestion of treating "inside the arcades" does not specifically defines how close to the arcades the grid should reach. This linguistic ambiguity may introduce a variability across predominantly mono-centric studies leading to variable study outcomes. In summary, there are numerous factors that potentially influence the study and treatment outcomes with subthreshold laser that needs to be understood and quantified in order to correctly design studies using subthreshold laser. Some of the parameters can be compensated for in the study design (such as fixing the laser parameters or restricting the use of a particular manufacturer). For other parameters, especially the plan design, it is unclear if differences are present and may potentially need to be considered when conducting clinical trials.

Consequently, the objective of this study is to assess and quantify the variability of subthreshold laser treatments utilizing a laser system capable of tracking confluent, non-geometric (freeform) treatment plans. The knowledge about a potential presence of plan variability may lead to study designs compensating for this variability in future studies, in additional well known and quantifiable variability such as physical characteristics of the lasers itself future studies may need to consider, stratify or compensate also for the potentially existing variability in the actual plan design.

Methods

Study population

The image data used for participants' planning in this study was obtained from a retrospective study approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Ireland under ECM 4 (v) on 13/4/2021, aligning with the principles of the Declaration of Helsinki. The original study included patients who underwent laser treatment (either threshold or subthreshold) with the navigated retinal laser. Informed consent was obtained from all the patients to include their retrospective data in the study. For this pre-planned sub-study, we randomly selected patients meeting specific criteria, which included having a complete dataset of high-quality images. This irreversibly anonymized dataset comprised a thickness map from OCT, a fluorescein angiography (FA) image, and a fundus color image from the Navilas laser system of 10 DME and 10 CSCR patients.

Plan collection process

Retinal specialists were then invited to create subthreshold laser treatment plans using the Navigate App (OD-OS GmbH). This free online planning tool allows users to upload diagnostic images and facilitates the placement of both titration and treatment spots, allowing adjustments in treatment area directly on the diagnostic images. The operator can choose from either a color + FA image, color + OCT, or a combination of all three as the basis for the plan. Subsequently, the retinal specialists determine the exact location of the spots on the particular patient using a mouse or touchscreen. There was no training or consensus meeting before the retinal specialists planned the treatment with the purpose of reflecting the actual state of planning, rather than a potentially possible minimal variability. Other parameters such as duty cycle (DC), power, and pulse duration are typically selected during treatment; therefore, the Navigate App does not allow for presetting these parameters. The plan layout is then saved but remains concealed from other retinal specialists. The plans, along with additional participant information (Age, Gender, Region of residence, 10-point self-rated subthreshold laser experience scale), were anonymized and exported for subsequent evaluation. A classification of the submitted plans into either "panmacular" or "targeted" was done, and each plan was classified as either "covering fovea" or "avoiding fovea" by a masked reader.

Consensus/difference quantification

The absence of a standardized comparison of such patterns consisting of points for retinal laser plans prompted the development of quantifiable parameters for assessing differences in the submitted plans. In order to establish a well-defined and quantified metric, all submitted plans were transformed into a binarized image representation, and the planned grids were extracted as areas from these images through image dilation, as illustrated in Fig. 1a. The centroid (center of mass, red crosses in Fig. 1b) of each individual plan was then determined using image processing techniques, and corresponding coordinates were documented[16]. Subsequently, all plans per patient were merged to generate a comprehensive heat map, depicted in Fig. 1b. Contour lines outlining the areas planned by at least 25%, 50%, and 75% of the participants were overlaid, as demonstrated in Fig. 1c. Notably, all image processing procedures were executed using Python[17] programming language.A visual examination of the contour line map provided an initial insight into the level of agreement among participants. The distance between these lines emerged as a representative parameter indicating the degree of similarity in their planned treatment areas. The closer the contour lines, the stronger the agreement. To quantify this "distance" mathematically (lines being closer together or further apart), we computed the difference between the two contour lines. The area planned by at least 75% of the participants was subtracted from the area planned by at least 25% of the participants. This concept is visualized in Fig. 1c. The resulting value represents

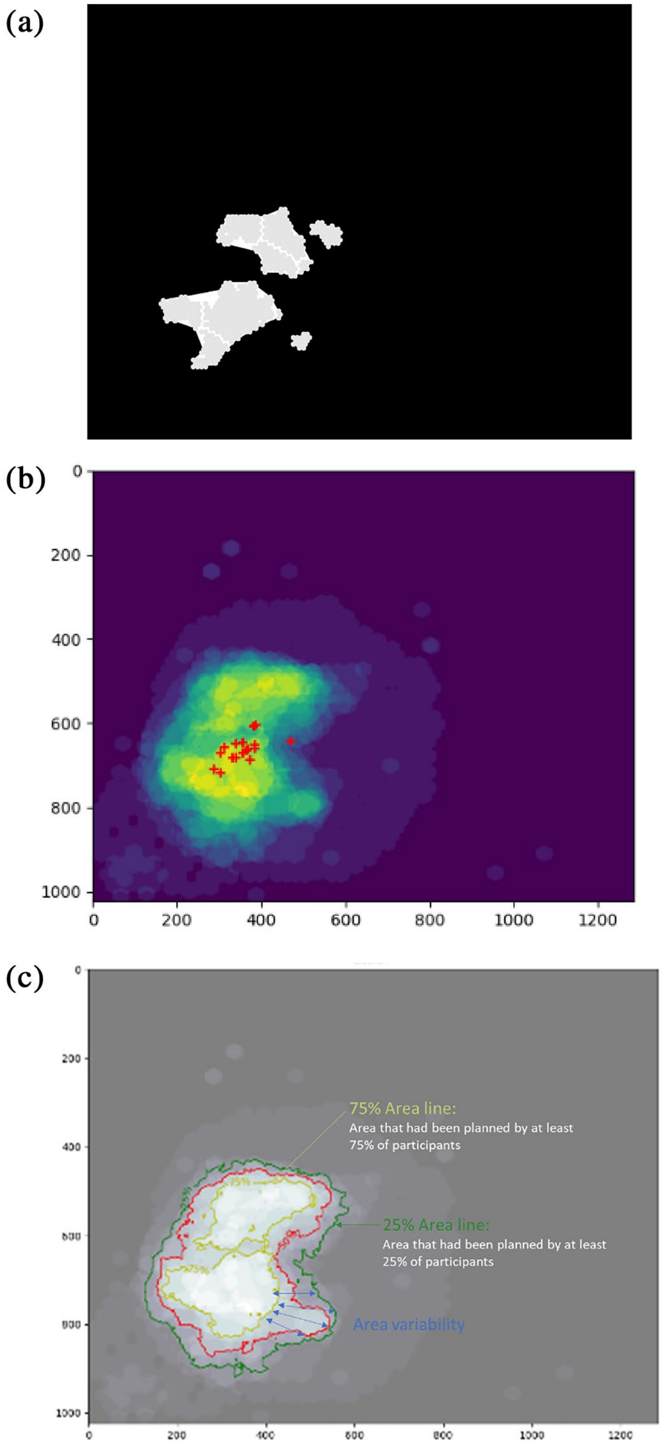

Fig. 1. Sample Images of image processing chain for extraction of plan area parameters (**a**) is an example of the area extracted of the sample plan of single participant after image dilation, (**b**) is the representative heat map of several participants for the same case, including red spots for the centroids, (**c**) is the representative heat map with contour lines for the same case.

the "area variability" (AV) in this study. A smaller AV value denoted a higher consensus among the plans, as the distance between the two contour lines is small.

Additionally, we calculated the median Euclidean distance in pixels between the centroid points derived from all plans for the same patient. This metric, referred to as "Centroid Distance" (CD), reflects the level of agreement concerning the treatment focus for a specific case. A smaller median distance signifies a greater concordance on the focus of treatment among the proposed treatment plans.

	Total	DME	CSCR
Number	20	10	10
Age (median, range)	66 (30–88)	69 (59–74)	50 (30–88)
Gender (m/f)	14/6	6/4	8/2
Disease type	–	8/10 NPDR 1/10 severe NPDR 1/10 PDR	5/10 referrals with unclear type 3/10 persistent 2/10 recurrent

Table 1. Patient characteristics. m–male, f–female, NPDR–non-proliferative Diabetic Retinopathy, PDR–proliferative diabetic retinopathy, DME–diabetic macula edema, CSCR–central serous chorioretinopathy.

Characteristics	All patients	DME	CSCR	*P*
Number of spots *Mean ± SD (CoV)*	335 ± 372	423 ± 409	261 ± 322	< 0.001
AV Distance 25 − 75% *Mean ± SD (CoV)*	9.8 ± 8.9%	12.5 ± 10.5%	7.02 ± 6.34%	0.075
CD *Mean ± SD (CoV)*	71.0 ± 37.5	72.9 ± 24.2	69.1 ± 48.8	0.6305

Table 2. Plan parameter overview per disease. DME: diabetic macular edema; CSCR: central serous chorioretinopathy; SD–Standard deviation; CoV–Coefficient of variation, statistical significance by Mann-Withney-Wilcoxon test, $p < 0.05$ is statistically significant; AV: area variability; CD: centroid distance.

Sample size and statistical considerations
A formal sample size calculation was not feasible for this study due to the absence of similarly designed studies and the novelty of treatment area definitions used in this study. Descriptive statistics were provided for all parameters. For subgroup comparisons, a Mann-Whitney-Wilcoxon test was employed to evaluate differences in the parameters within each group, after defining non-normal distribution of the CD and AV parameters, using the Shapiro-Wilk Test. A p-value of < 0.05 was denoted statistically significant.

Results
A cohort of 25 retinal specialists from eleven countries (Austria, France, Germany, Italy, Peru, Russia, Spain, Sweden, United Arab Emirates, Ukraine, United States of America), predominantly male (76%), with a median age of 43 years (ranging from 33 to 62), contributed a total of 412 plans for 10 DME and 10 CSCR patients. The demographic details of these patients are summarized in Table 1.

General plan styles
After excluding plans with single spots, 344 plans were evaluated. Among the participants, a slight majority (52%) self-assess their experience levels as high, with levels of 8, 9, or 10.

Of these, 72% plans employed a combination of OCT and FA images, while 9% exclusively used OCT, and 19% exclusively used FA, indicating no clear preference for a specific image combination. There were 7 different plan classifications, with only 2 participants (8%) opting for a panmacular approach. Notably, both participants initially using this approach transitioned to a more targeted style for at least one patient, resulting in the panmacular approach being utilized in 9.3% of plans. Additional to the panmacular plan styles, the following variants of a targeted style (312 plans from 25 participants) plan patterns included:

- four participants combining spaced and confluent grids in 8 plans with or without single spots
- Fourteen participants using confluent grids in 176 plans with or without single spots.
- Sixteen participants using spaced grids in 128 plans with or without single spots.

Additionally, 30 plans (9.6% of targeted plans and 8.7% of all plans) incorporated single spots, added by 10 participants. A majority of 89% of the plans exhibited an avoidance of the foveal area. Additionally, 30 plans (9.6% of targeted plans and 8.7% of all plans) incorporated single spots, added by 10 participants. A majority of 89% of the plans exhibited an avoidance of the foveal area.

Overall variability analysis
Table 2 provides numerical parameters for the overall plans, as well as separate values for DME and CSCR. In the comprehensive evaluation, the mean CD value is 71.0 ± 37.5 across all cases, equivalent to approximately 640 µm, representing half the size of the optic disc. Figure 2 illustrates the differences between the disease groups. While there is an observable difference in the mean Centroid Distance (CD) values between CSCR and DME, indicating that CSCR patients, on average, exhibit a smaller distance of CDs, reflecting more consistency in the treatment focus, this difference does not attain statistical significance. Interestingly, the CD values within the CSCR groups exhibit greater variability around their mean compared to the CD value of the DME patients.

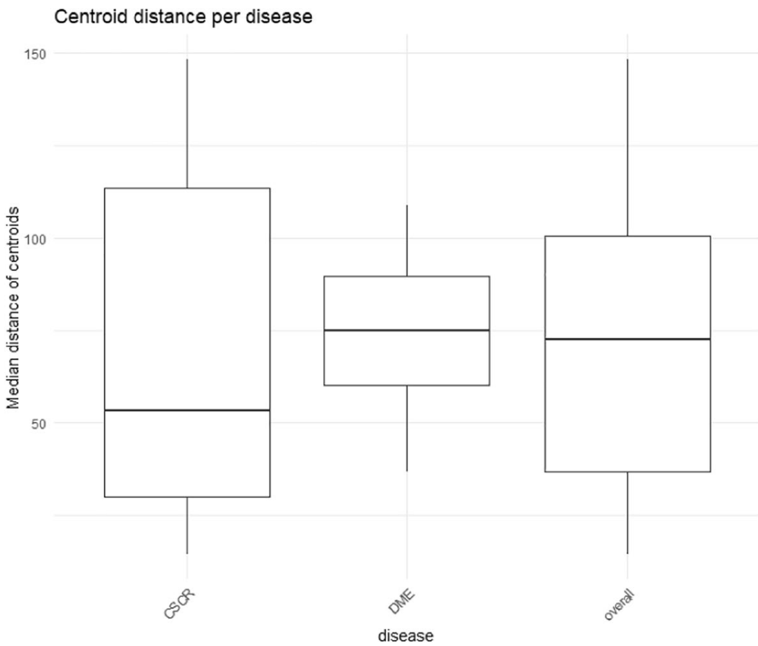

Fig. 2. Centroid Distance per disease.

This observation suggests that, while overall consistency is generally lower in DME, CSCR patients display a spectrum, with some being very "consistent" and others very "inconsistent" regarding the treatment focus.

Figure 3 visually represents the treatment areas across all patients. The red dot indicates the area (in percentage of total pixels) covered by at least 50% of participants. The upper whisker end represents the area covered by at least 25% of participants, while the lower whisker end shows the area covered by at least 75% of participants.

The length of the whisker illustrates the Area Variability (AV)—the difference between the most and least agreed-upon treatment areas. A longer whisker indicates a greater disparity in the areas planned by "all" (75%) versus "some" (25%) participants, suggesting more variability in planning. Conversely, a shorter whisker means closer agreement among participants, indicating a smaller difference between the 75% and 25% contour lines.

Across all patients, the AV averages $9.8 \pm 8.9\%$. The graph reveals that the lower whisker length (the difference between the areas planned by 50% and 75% of participants) is significantly shorter, with a difference of $3.2 \pm 3.1\%$, compared to the upper whisker length (the difference between the areas planned by 25% and 50% of participants), which is $13 \pm 0.12\%$.

This suggests that while participants generally agreed on the central treatment area (the "hot spot"), the extent of the surrounding area varied significantly, with fewer participants including these outer regions in their plans.

Experienced based review of all plans

In the subgroup analysis, participants were classified into two experience levels: "lower," encompassing those with a self-rated experience level of seven or below, and "higher" for those with a self-rated experience level of eight or above. This categorization resulted in two well-defined and relatively equal-sized cohorts.

Upon reviewing the cohort with lower experience levels, a notable distinction is apparent exclusively in the AV parameter, as depicted in Table 3. The group with lower experience demonstrates a higher AV value in contrast to the "higher" experience group.

Panmacular only review

There was insufficient data for the "panmacular" subgroup to compare both groups using the parameters AV and CD. However, since the panmacular style is always centered around the macula, the actual planned area serves as an alternative measure for assessing variability in this plan style. For the two operators, the area covered across all patients was 20.5% and 26.4% of the total image area. Within each operator, the planned area varied from 9 to 48% of the image. When comparing the two operators, the differences in the planned area ranged from 4 to 33% of the image, with an average difference of 13%. Due to the small sample size, no statistical differences were calculated.

Discussion

A potential cause for variable outcome in clinical studies using thermal subthreshold laser[10] and threshold laser treatments[2,3] are likely to arise from many various parameters, such as physical laser characteristics. The variability of treating plans is one element potentially contributing, that had not been assess so far for subthreshold laser strategies. Therefore, this study assessed the variability of subthreshold laser treatment plans independently from other parameters. In our cohort of treatment plans, a predominant plan style emerged, with

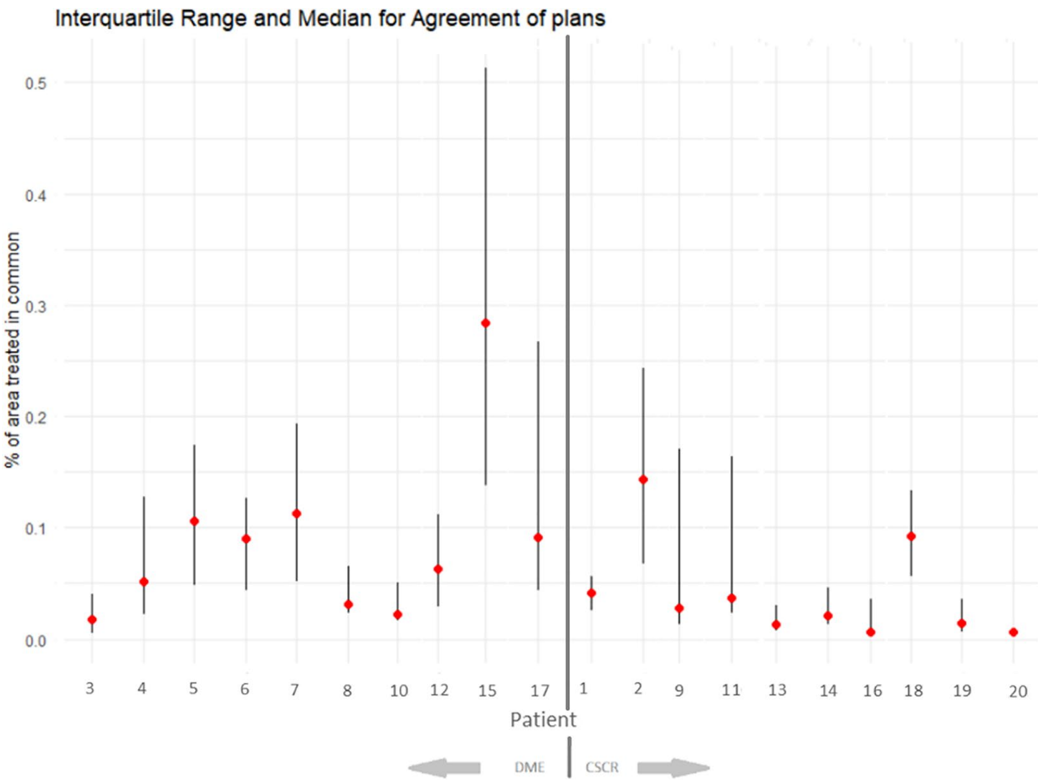

Fig. 3. AV per patient sorted by disease. The percentage of the whole image area covered by 25% (upper end of the line) , 50% of participants (red dot) and 75% of the participants (lower end of the line) is shown. The distance between the lower end line and the upper end of the line is the Area Variability (AV) .

Characteristics Number of particpants/plans	Lower experience 12 / 131	Higher experience 13 / 213	*p*
Number of spots *Mean ± SD (CoV)*	331. ± 401. (1.2)	288. ± 332. (1.2)	0.7258
AV Distance 25 − 75% *Mean ± SD (CoV)*	24% ±22% (0.92)	8.6% ±7.1 (0.83)	0.007331
CD *Mean ± SD (CoV)*	75.9 ± 48.1 (0.63)	55.9 ± 34.0 (0.61)	0.2012

Table 3. Plan parameter overview grouped by level of experience. SD–Standard deviation; CoV–Coefficient of variation, statistical significance by Mann-Withney-Wilcoxon test.

92% adopting a targeted approach. Notably, a considerable number of experts utilized a spaced pattern, avoiding the subfoveal area, and a minority incorporated single spots. The concurrent use of OCT and FA images was observed to be advantageous for planning with 75% of the participants.

Quantifiable parameters, including Centroid Distance (CD) and Area Variability (AV), revealed significant variability. The CD, representing the treatment focus, is mathematically defined as the median distance between the centroids of all plans for the same patient, averaging 71 pixels (approximately half the size of the optic disc). The distance between the contour lines, denoting Area Variability, averages 9.8% and serves as a representative measure for the variability in the treated area. The AV underscored a notable "hot spot" with high agreement for treatment (as seen in Fig. 3 by the length of the whiskers), yet the extent of treatment surrounding this area exhibited higher variabilities, particularly evident in CSCR cases. Subgroup analysis disclosed more consistent plans from experienced surgeons compared to those with less extensive experience, with the CD and AV parameters being better for the higher experienced groups. This indicates that Ophthalmologists undergo a learning curve leading to "more effective" laser plans.

Notably, no prior literature has examined the variability in subthreshold laser plans, and the parameters established in this study are unique. However, attempts to assess variability in threshold laser plans by van Dijk et al. and Kozak et al. revealed substantial differences among operators in threshold laser applications[2,3], aligning with the variability in subthreshold laser plans observed in our study. Similarly, no study has compared different experience levels for laser treatment outcomes or plans. Nonetheless, Starnawska et al. compared the accuracy of laser applications between a non-experienced operator and a highly experienced operator using the Navilas laser[18]. While this study found no difference when using a navigated laser, it was initiated upon the assumption of smaller application accuracy with less experience. In our study, accuracy is not the primary outcome; rather, we focus on consistency, which is lower in less experienced operators compared to their more experienced counterparts, aligning with the base assumption by Starnwaska et al. of seeing quality differences upon variable experience levels. Consistently, an analysis of the time required for laser application revealed a learning curve, especially when transitioning from a slit lamp-based laser to a navigated laser concept[19]. Our outcome measures offer a preliminary understanding of the variability in treatment location and extent. Although, this study is only an initial assessment it highlights the importance of considering different treatment plan styles in future clinical studies. Other approaches for assessment of the plan styles (e.g. comparing to one plan as "ground truth") had been considered, but withdrawn, particularly since the definitive "ground truth" for the optimal treatment plan remains unknown. Though, the existing variability in subthreshold plans shown in this analysis emphasizes the need for caution in clinical studies. Although, the discussion about the true impact of different plans on clinical outcomes remains open, yet the substantial variability of the area treated by different ophthalmologists as represented by the AV and CD measure in this study could be a potential factor to influence clinical treatment outcomes. It is evident that the "Truth" about the optimal plan remains unknown, also necessitating large-scale trials with consistent plan styles for meaningful comparisons. One of the few studies comparing different plan styles is by Lavinsky et al.[20], who contrasted an ETDRS grid-style treatment with a confluent concept. They identified a confluent (high-density) pattern as more effective. Another study by Alharif et al. compared a concept labeled "targeted directly to the edematous area" with "directly targeting peripheral areas," noting a significant improvement in both groups at 6 months, with the "peripheral group" demonstrating a faster improvement compared to the directly targeted group[21]. However, the absence of visualized treatment plan layouts raises questions about the consistency between the "peripheral approach" and the "panmacular approach" described by the LIGHT group, and whether the "directly targeted approach" is equivalent to the "targeted approach" as described by the SOLS group. Even though the linguistic ambiguity does not allow a correlation to the SOLS and LIGHT concept, it emphasizes, that the subthreshold laser plan style also impacts the treatment outcome.

The development of the quantifiable parameters in this study opens avenues to assess the success of training measures. If CD and AV parameters show improvement after the training, it may indicate successful training. Alternatively, the contour line heatmap of a particular case may be shown upon request in the Navigate App, to allow the resident a self-check for the planning and critically appraise the "average" plan of a well experienced laser group.

The study's strengths lie in the robust, quantifiable parameters, a large number of participating experts, and a realistic planning environment using the Navigate App. However, the lack of panmacular plans represents a limitation, leaving the extent of variability in this approach uncertain and prevented a comparison of both approaches, although the plans from the two participants also demonstrate an ambiguous interpretation of panmacular approach description. Another limitation for the subgroup analysis, however, is the number of participating experts. Although we collected feedback from 25 participants, a post-hoc power calculation for group comparisons indicates insufficient power for a subgroup comparison. Therefore, further data collection would be necessary to compare two groups of participants. Future research is needed to analyze the impact of different laser types and devices used prior to this study. Although most participants reported experience with the Navilas Laser System, they also had experience with other subthreshold laser systems. The influence of prior experience with specific laser systems on treatment variability warrants further investigation. Analyzing these factors will help understand their contribution to variability in treatment plans. Future research should also explore in detail how spot placements might correlate with structural changes observed in OCT, FA, or fundus images. More sophisticated analysis approaches, including the use of machine learning and larger datasets, is necessary to investigate the sources of this variability more thoroughly.

In summary, our findings suggest a need for a more nuanced discussion about treated areas to enhance understanding and reduce variability. While our paper does not discuss the effectivity of a specific plan, plan extend or methods, we were able to show both established approaches are subject to variability, potentially influencing the clinical outcome. Future studies should aim to minimize variability in the planning, especially when conducting multicentered trials, and explore the impact of different plan strategies on treatment outcomes in different diseases. This plan standardization can be supported through digital pre-planning with a modern, navigated laser system, by centralized treatment plan outline or by more thorough visualized education. Broader expert inclusion in data collection may further refine our understanding of optimal plans, particularly when including the most experienced subthreshold laser specialists.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions
UR, JC: concept and design, wrote the manuscript text, prepared the figuresCDR, SA, EN, IK: wrote the manuscript and prepared the figuresAll authors reviewed and approved the manuscript.

Declarations

Competing interests
Ulrike Rahn: Consultant to OD-OS GmbH. Jay Chhablani: Consultant to OD-OS. Christian-Dennis Rahn: no competing interests, no financial disclosures. Supriya Arora: no competing interests, no financial disclosures. Eugene Ng: no competing interests, no financial disclosures. Igor Kozak: no competing interests, no financial disclosures.

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