PROTOCOL TITLE: Micropulse for suppression of diabetic macular edema "PULSE STUDY"

1) Protocol Title

microPUlse Laser for Suppression of diabetic macular Edema (PULSE Study)
NCT03519581

2) Author of Protocol

X UC Davis Researcher
☐ Researcher from other institution
☐ Private Sponsor
☐ Cooperative Group
X Other: UCD Resident

3) IRB Review History

None

4) Objectives

The purpose of this study is to analyze the effect of subthreshold micropulse diode laser in the treatment of central-involving diabetic macular edema in eyes with good visual acuity defined as 20/32 or better on ETDRS testing, compared to observation alone (sham treatment).

We hypothesize that eyes treated with subthreshold micropulse diode laser will demonstrate either a significant improvement or stabilization of visual acuity at 12 and 24 months, or a significant delay in vision loss to 20/40 or worse, requiring initiation of anti-vascular endothelial growth factor (anti-VEGF) therapy.

5) Background

Diabetic retinopathy is one of the most common complications of diabetes and diabetic macular edema (DME) is one of the most common causes of vision loss in diabetes.[1] Various treatment strategies for diabetic macular edema include focal or grid laser, anti-vascular endothelial growth factor (anti-VEGF), and corticosteroid treatments.[1,2] The Early Treatment of Diabetic Retinopathy Study (ETDRS) in the 1980s and 1990s, which included patients with moderate to severe non-proliferative diabetic retinopathy (NPDR) or mild proliferative diabetic retinopathy (PDR), revealed that focal photocoagulation is effective in reducing the risk of moderate vision loss from DME by 50%.[3,4] Focal laser was also shown to be more effective with fewer side effects than intraocular steroids such as triamcinolone acetonide in the treatment of DME in eyes with visual acuity of 20/40 or worse, making focal laser a benchmark against which other treatments were compared.[5] Results of the Diabetic Retinopathy Clinical Research network (DRCR.net) Protocol-I established a new benchmark and revealed that in eyes with DME and visual acuity of 20/32 or worse, intravitreal anti-VEGF therapy using ranibizumab with prompt or deferred focal laser was superior to focal laser alone.[6] More recently, the RIDE and RISE studies revealed that in eyes with visual acuity of 20/40 or worse, patients treated with ranibizumab had 15 or more letters of visual acuity gain compared to sham injections.[7] Current treatment guidelines for DME are largely derived from DRCR network Protocol T, which has addressed the relative efficacy of various anti-VEGF agents in improving visual acuity, and decreasing central foveal thickness[8,9]. However, all major clinical trials in management of DME

have only addressed eyes with visual acuity of 20/32 or worse. To date, there are no consensus on the best treatment approach for center-involving DME with good visual acuity (20/25 or better). The DRCR.net Protocol V is an ongoing randomized controlled study to determine if prompt anti-VEGF therapy can preserve vision in eyes with DME and good visual acuity of 20/25 or better. While this study has not yet been completed, intravitreal anti-VEGF therapy is not without risk, some of which include endophthalmitis, elevated intraocular pressure, and systemic vascular events. We hypothesize that early management of DME with good visual acuity requires treatment with a less invasive strategy.

A recently-developed treatment for DME is subthreshold micropulse laser (SML). In contrast to focal laser, SML delivers laser energy in a "chopped" fashion allowing the tissue to cool between pulses to eliminate thermal injury to the retina[10]. Previous studies have shown the superiority of SML to conventional focal/grid laser photocoagulation in improving visual acuity.[2,11,15] In eyes undergoing anti-VEGF therapy for DME, SML may reduce the frequency of injections. Unlike traditional "focal" laser therapy which are associated with macular scarring and choroidal neovascularization, SML are not associated with any of these complications, even after multiple treatments. While some physicians employ SML for treatment of DME in eyes with good visual acuity, due to the safety of this laser, there are no clear evidence supporting their use. Hence, there remains no consensus for standard of care for whether observation, anti-VEGF injection, focal/grid laser, or SML should be used for eyes with visual acuity of 20/25 or better. As most patients with good visual acuity are reluctant to undergo an intraocular injection which has greater risks associated such as endophthalmitis, vitreous hemorrhage, or retinal detachment, we seek to assess the potential benefit of SML laser alone vs. observation (sham) in this selection of eyes in preserving vision and anatomy.

The ETDRS study employed biomicroscopy, fundus photography, and fluorescein angiography as the standard modalities for assessing the presence and extent of DME.[3] Since that time, newer methods are available to characterize DME including optical coherence tomography (OCT), fundus autofluorescence (FAF), and OCT angiography (OCT-A).[12] Similarly, while visual acuity testing has been the most common method for functional assessment, newer methods such as microperimetry are being utilized to evaluate and quantify functional outcome by means of retinal sensivity.[12,13] The evaluation of retinal sensitivity is done through visual field testing. However, traditional visual field tests are not sensitive enough to identify small scotomas, especially when fixation is altered by macular edema. Microperimetry is a visual field test that has a fundus tracking system allowing it to overcome fixation instability. Furthermore, the stimulus used to assess retinal sensitivity is projected in the identical retinal area during the initial and subsequent examinations, thereby allowing identification of small scotomas and eccentric fixation. This is critical in preserving fixation when treating the macular edema with photocoagulation[12]

Microperimetry has gained recent popularity in assessing functional impairment in patients with DME, allowing a correlation between retinal morphology (macular thickness) and retinal sensitivity.[12,14] For example, Verma et al have shown decreased retinal sensitivity correlating with decreased foveal thickness in individuals with diabetes without diabetic retinopathy.[13] Others have shown improved retinal sensitivity in eyes with DME after SML treatment when assessed by microperimetry.[15] These studies underscore the importance of microperimetry in quantifying visual function in eyes with DME, particularly in eyes with good visual acuity where an improvement in visual acuity may not be readily discernable.

Our goal in this study is to assess the effect of subthreshold micropulse diode laser in eyes with DME and good visual acuity defined by vision of 20/32 or better based on ETDRS testing. We hypothesize that subthreshold micropulse diode laser will significantly improve visual acuity, retinal anatomy, and retinal sensitivity on microperimetry, and also prevent vision loss by delaying the need for anti-VEGF therapy compared to observation alone.

6) Inclusion and Exclusion Criteria

Subjects will be recruited from patients seen at the UC Davis Eye Center retina clinic who are willing and eligible to participate based on our inclusion criteria.

Inclusion Criteria:

1. Age >=18 years
2. Type 1 or type 2 diabetes mellitus
3. Clinical evidence of center-involved DME confirmed on OCT, and defined by OCT Central Subfield (CSF) thickness at the time of randomization by the following:
    a. Zeiss Cirrus: 275µ in women, and 290µ in men
    b. Heidelberg Spectralis: 290µ in women, and 305µ in men
4. Best corrected visual acuity of 20/32 or better on ETDRS testing

Exclusion Criteria:

1. Macular edema from causes other than DME
2. An ocular condition is present such that in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (i.e/foveal atrophy, pigment abnormalities, dense hard exudates)
3. An ocular condition is present other than DME which may contribute to macular edema (i.e/vein occlusion, ERM, uveitis, RP, etc…).
4. Cataract that in the opinion of the investigator may alter visual acuity throughout the course of the study
5. History of prior laser or other surgical, intravitreal, or peribulbar treatment for DME in the study eye within the prior 6 months.
6. More than 4 prior intraocular injections for treatment of DME at any time
7. More than 1 prior focal/grid macular photocoagulation session for treatment of DME at any time
8. History of topical steroid or NSAID treatment within 30 days prior to randomization
9. History of PRP within 4 months prior to randomization or anticipated need for PRP in the 6 months following randomization.
10. Any history of vitrectomy.
11. History of major ocular surgery (cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following randomization
12. History of YAG capsulotomy performed within 2 months prior to randomization.
13. Aphakia
14. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis

7) Study Timelines

- The duration of an individual subject's participation in the study will be two years which will include at least 10 total visits at various time points including on the day of enrollment, followed by 1, 3, 6, 9, and 12, 15, 18, 21, 24 months after the day of enrollment
- The duration anticipated to enroll all study subjects is 1 year
- The estimated date for the investigators to complete this study is December 2023
- 36 eyes will be enrolled based on power calculations for 80% power assuming at least 40% of eyes monitored by observation alone will experience vision loss to 20/40 or worse, and that SML treatment will reduce that value to 15%, using a 2:1 ratio for randomization (2 treatment : 1 observation (sham)). The ETDRS study showed that among eyes with good visual acuity (20/25 or better), 40% will experience a visual acuity decrease by 5 letters or more. We assume a higher rate among eyes with 20/32 or better.

8) Study Endpoints

Primary outcome:

- Proportion of patients with vision loss to 20/40 or worse on ETDRS testing on two visits ≤28 days apart at 12 and 24 months.
- Mean time to vision loss to 20/40 or worse on ETDRS testing on two visits ≤28 days apart

Secondary Outcomes:

- Mean change in visual acuity, low luminance visual acuity and contrast sensitivity at 3, 6, 9, 12, 15, 18, 21, and 24 months from baseline
- Mean change in central macular thickness (CMT) on OCT at 3, 6, 9, 12, 15, 18, 21, and 24 months from baseline
- Mean change in retinal sensitivity assessed by microperimetry at 3, 6, 9, 12, 15, 18, 21, and 24 months from baseline
- Percentage of subjects with visual acuity loss (including low luminance visual acuity and contrast sensitivity) of ≥ 5 letters at 12 and 24 months
- Percentage of subjects with at least 10 and 15 letter gain or loss at 12 and 24 months
- Visual acuity area under the curve at 12 and 24 months
- Number of SML treatments received at 12 and 24 months
- Number of anti-VEGF treatments received at 12 and 24 months
- *Any safety concerns documented during the study*

9) Procedures Involved

This is a randomized, controlled clinical trial comparing subthreshold micropulse laser versus sham laser treatment for eyes with diabetic macular edema with good visual acuity of 20/32 or better. After signing written consent and enrolling in the study, patients will be randomized to receive either subthreshold micropulse laser treatment or no treatment (sham). Randomization will occur as a ratio of 2:1 and will take place during the clinic visit. A block randomization scheme will be created before the study begins to ensure appropriate treatment allocation among the two groups. At the time of randomization, only one eye will be randomized to either the treatment or observation. If both eyes meet the inclusion criteria, one eye (worse eye) will be assigned to the treatment group and the fellow eye to the sham treatment group. Subjects selected for the study will then undergo a complete ophthalmic examination, including measurements of best corrected visual acuity, low luminance visual acuity, contrast sensitivity (using ETDRS testing with a masked coordinator), intraocular pressure, slit lamp exam including documentation of lens status, and dilated funduscopic exam with standard dilating agents used at the UC Davis Eye Center. Subjects will then undergo baseline imaging with SD-OCT and fundus autofluorescence (FAF) using the Spectralis OCT+SLO instrument (Heidelberg Engineering, Heidelberg, Germany) and Optos (Optos Inc.). The Optos imaging system will only be used as a back up to the Heidelberg, as well as microperimetry testing using Nidek MP-1 instrument (Padova, Italy). Both the use of OCT, FAF, and microperimetry testing are within the standard of care for the management of DME.

For OCT and FAF, a lubricating artificial tear drop may be used on subjects with dry eyes to enhance image quality as is routinely done. Each eye will have 3-4 images acquired, which will take approximately 30-45 seconds for each eye. OCT imaging must include at least one high resolution scan across the fovea, and central macular thickness measured as determined using the OCT instrument's algorithm. FAF imaging must include the entire macular region through which the micropulse laser treatment will be applied.

For microperimetry, a built-in fundus camera is used to focus on the patient's retina and fundus tracking ensures fixation stability. As the patient perceives the stimulus, they press a trigger which is then recorded similar to other widely used perimetry tests (Humphrey visual field test). Testing will take approximately 3-4 minutes per eye.

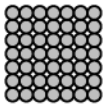
Qualified ophthalmic personnel (physicians, certified ophthalmic technicians, and certified ophthalmic photographers) under a study personnel supervision will administer all eye drops, perform the ophthalmic exam, and capture images on the Spectralis OCT and MP-1 microperimeter.

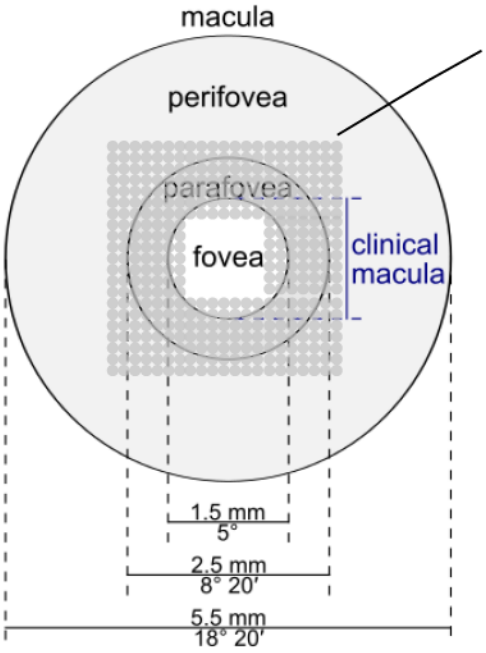
The subjects in the treatment arm will be treated on the day of randomization by SML photocoagulation using the Iridex IQ577 laser unit with TxCell scanning laser delivery system. Treatment will involve the following steps:

1. Confirm the patient's identity and eye to be treated using a standard pre-procedure time-out. Confirm the patient's eye is dilated and comfortably postured at the slitlamp for treatment.
2. Ensure the laser aiming beam is in focus on the retinal surface.
3. Confirm the IQ 577 laser system is in CW treatment mode using the laser's Preset function. Using a contact lens with an approximate 1x laser magnification for macular laser treatment (e.g. Volk Area Centralis®) and a 200 µm spot, perform the test spot in continuous wave (CW) mode with a 200 ms duration in the minimally edematous macula > 2 DD from foveal center.
4. Start at 50 mW and titrate power upwards in 10 mW increments – moving to a new area each time – until a barely visible tissue reaction is seen. If a reaction is evident with 50 mW, do not increase the power. Note the threshold power.
5. Switch the laser to MicroPulse mode at 5% duty cycle using the laser's Preset function and adjust the power to 4 times the power achieved in the CW pre-treatment test spot.
6. Deliver a single spot outside the macula to confirm laser system is in MicroPulse mode.
7. Adjust the TxCell Scanning Delivery System to a 7x7 grid with zero-spot spacing.
8. Deliver high-density applications as indicated in FIGURE 1: three 7x7 grids above and below the fovea (250 µm from its center) and one 7x7 grid at each side (temporal and nasal) of the fovea (250 µm from its center); if edema is present outside this area, treat it too.

FIGURE 1

TxCell 7 x 7 grid pattern (49 spots)





9. Confirm that the patient can detect at least finger-counting vision after laser procedure.

Those in the sham treatment arm will undergo the same set up procedures as described above, however, no actual laser treatment will occur. Subjects will then return to the clinic for repeat ophthalmic exam, OCT imaging, and microperimetry at 1 month, 3 month, 6 month, 9 month, 12 month, 15 month, 18 month, 21 month and 24 month time points, which is similar in frequency as standard of care. Patients in the treatment arm are eligible for repeat SML laser at any subsequent visit if there is any decline in vision (1 or more ETDRS lines) or worsening in edema (>10% increase), at the discretion of the treating physician. If vision declines to 20/40 or worse at any study visit, patients in the treatment arm will undergo repeat treatment with SML laser, while those in the sham arm will undergo repeat sham laser.

If the patient demonstrated 20/40 or worse ETDRS visual acuity at any study visit, he or she will be required to return within 28 days for repeat ETDRS visual acuity testing, ophthalmic exam, OCT imaging, and microperimetry. If the patient demonstrated 20/40 or worse ETDRS visual acuity at this repeat visit, then the patient will have reached study endpoint and be considered treatment failure. At that visit, patients may be given any combination of intravitreal anti-VEGF injection (preferred based on DRCR.net protocol I and protocol T), focal/grid laser, repeat SML treatment, or intravitreal steroid injection, based on the discretion of the investigator. After study endpoint (visual acuity loss to 20/40 or worse), patients may be treated on a monthly, pro re nata (PRN), or "treat-and-extend" basis based on the individual investigator's preference. Patients are still required to continue with study visits, but any additional visits or treatments, although still documented, will be considered off-study.

All data will be analyzed in accordance to the "intention-to-treat" principle.

10) Data and Specimen Banking

All data will be stored on secured network drives at UC Davis and information properly de-identified (see below).

11) Data Management and Confidentiality

Captured OCT images and microperimetry reports will be analyzed by the UC Davis Reading Center in a masked fashion. Data analysis will be performed *by study staff, and s*tandard statistical methods will be used in the analysis of data collected. Subjects will be de-identified via the use of a separate secure document correlating subjects' UC Davis medical record numbers with a study ID assigned for the sole purpose of this study. Recorded data will be stored in a password protected excel file. Only the investigators will have access to these files. All study personnel will be Biomedical and GCP CITI certified and will be maintained by the research coordinating staff.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects

Study data will be analyzed with the assistance of a CTSC biostatistician to determine if any safety concerns exist in respect to disease progression between the treatment arm and the sham arm. Analysis will be performed at the timepoint when 12-month follow-up data has been

acquired from at least 10 eyes randomized to each group (laser treatment and sham). A summary of the findings will be prepared and utilized to determine if changes in study conduct or study termination is necessary.

13) Withdrawal of Subjects

Any patient wishing to withdraw from the study at any time during the study will be able to do so. They would return to our clinic as they normally would for future care, however any data obtained from future their visit will not be included in the study.

14) Risks to Subjects

For the ophthalmic examination, OCT imaging, and microperimetry, there are no known risks to the subject beyond what is normal for standard ocular examination and testing used in routine patient visits at the UC Davis Eye Center. The limits for safe ocular exposure to laser light have been well established and are documented by the American National Standards Institute, ANSI Z136.1-2007. The most conservative ANSI standard for maximum permissible exposure, MPE, for 870nm light is 750mW assuming full pupil intrabeam viewing (7mm pupil aperture) for long exposure times (up to 8 hours). Exposure in our study protocol will not exceed this well-established limit. The Spectralis SD-OCT unit has a built-in timer that prevents the unit from imaging for more than 5 minutes cumulatively during a single patient encounter, making it effectively impossible to expose the patient to unacceptable levels of light.

The risks associated with the use of subthreshold micropulse diode laser are much reduced compared to the standard continuous wave laser which is used in the treatment of retinal edema with visual acuity that is equal to or worse than 20/40 on the Snellen chart. Standard continuous wave focal laser treatments are associated with risks including early and late visual loss aggravation of macular edema (ME) sub-retinal fibrosis, choroidal neovascularization, visual field loss, loss of color vision, metamorphopsia, and progressive expansion of the laser scars into the fovea[16]. However, the use of the subthreshold micropulse diode laser limits these standard risk factors by utilizing lower energy intensity and its "chopped" delivery method.[17] Multiple studies have demonstrated the safety of subthreshold micropulse laser compared to standard continuous wave laser in the treatment of macular edema using various imaging modalities. There have been no detectable changes noted in eyes treated with subthreshold micropulse diode laser on OCT, fluorescein angiography (FA) or fundus autofluorescence (FAF).[15,17,18] This has also been corroborated by histologic studies in which SML was noted to treat tissue without damage to the neurosensory retina.[10] Others have also demonstrated repeatability of SML treatment without detectable structural or functional damage[16,17,19]. In a prospective randomized clinical trial, Vujosevic et al. compared the safety of SML versus modified ETDRS green laser photocoagulation. They have shown that retinal sensitivity increased, and fundus autofluorescence imaging revealed no changes at one year follow up in eyes with DME even after retreatment with SML, whereas those treated with standard continuous wave laser revealed areas of hyperautofluorescence and decreased retinal sensitivity. The mean number of treatments was 2.03±0.75 in the SML group.[15] Moreover, Luttrull et al. have shown that 15 out of 39 eyes with DME and visual acuity better than 20/40 treated with SML required retreatment, yet no

evidence of laser effect or injury was noted to the retinal pigment epithelium (RPE) or neurosensory retina by any imaging modality including infrared fundus photography, red-free fundus photography, fundus autofluorescence, fluorescein angiography, or SD-OCT at any time in any eye postoperatively, other than reduction in the retinal thickness.[20] These studies underscore the safety of micropulse laser even in the setting of their repetitive use.

Micropulse laser for the treatment of DME in pregnancy has been found to be a safe option. Multiple studies and papers have included the use of laser in pregnant women. First-line treatments for DME in pregnancy are and should remain blood glucose control and laser. [21]

To date, there is no standard of care regarding treatment of macular edema in eyes with visual acuity of 20/32 or better; thus there is no associated risk for those patients randomized to the sham treatment group unless visual acuity drops to 20/40 or worse. Patients in the sham treatment arm of the study will be monitored on routine follow up visits and treated in accordance with standard practice guidelines if necessary.

15) Potential Benefits to Subjects

The proposed study may directly benefit its participants if SML indeed reduces risk of vision loss in patients with DME and good visual acuity.

16) Multi-Site Research

This is a single-site study

17) Community-Based Participatory Research

This is not a community-based participatory research.

18) Sharing of Results with Subjects

Results of the study related to individual subjects will be shared upon their request. Collective study results can be shared with study subjects however with de-identified data only, such that none of the participants can be identified.

19) Prior Approvals

None

20) Provisions to Protect the Privacy Interests of Subjects

All subjects retain the right to interact with any member of the medical and non-medical team. Patients may elect to only interact with the investigators of the study. Study staff will be available during the examination at all times to address any of the questions or concerns that the study subjects may have. The data obtained during the course of the study will be stored on password protected files and accessible only to the research investigators approved on the study

21) Compensation for Research-Related Injury

The research does not involve more than minimal risk to subjects

22) Economic Burden to Subjects

Participation in the study does not incur any additional costs to the study subjects. The cost of the micropulse laser treatments and SD-OCT are all part of standard of care for patients with retinal edema, which will be charged to subjects as part of their medical care. If repeat imaging is needed beyond what is considered standard of care, it will be covered by the study. Those receiving the "sham" treatment will not be billed for a laser treatment.

23) Drugs or Devices

This research study does not involve investigational drugs or devices. The eye drops, Heidelberg Spectralis SD-OCT device, and the IQ 577 laser device, with continuous-wave and MicroPulse treatment modes, are all used in standard of care.

1. Murakami, T. & Yoshimura, N. Diabetic Macular Edema. **2013,** 505–510 (2013).
2. Fazel, F., Bagheri, M., Golabchi, K. & Jahanbani Ardakani, H. Comparison of subthreshold diode laser micropulse therapy versus conventional photocoagulation laser therapy as primary treatment of diabetic macular edema. *J. Curr. Ophthalmol.* **28,** 206–211 (2016).
3. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch. Ophthalmol. (Chicago, Ill. 1960)* **103,** 1796–806 (1985).
4. Group, E. T. D. R. S. R. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* **98,** 766–85 (1991).
5. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* **115,** 1447–9, 1449–10 (2008).
6. Diabetic Retinopathy Clinical Research Network *et al.* Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* **117,** 1064–1077.e35 (2010).
7. Nguyen, Q. D. *et al.* Ranibizumab for diabetic macular edema: Results from 2 phase iii randomized trials: RISE and RIDE. *Ophthalmology* **119,** 789–801 (2012).
8. Diabetic Retinopathy Clinical Research Network *et al.* Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N. Engl. J. Med.* **372,** 1193–203 (2015).
9. Wells, J. A. *et al.* Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology* **123,** 1351–9 (2016).
10. Yu, A. K. *et al.* The comparative histologic effects of subthreshold 532- and 810-nm diode micropulse laser on the retina. *Investig. Ophthalmol. Vis. Sci.* **54,** 2216–2224 (2013).
11. Lavinsky, D. *et al.* Randomized clinical trial evaluating mETDRS versus normal or high-

density micropulse photocoagulation for diabetic macular edema. *Invest. Ophthalmol. Vis. Sci.* **52,** 4314–23 (2011).

12. Midena, E. & Bini, S. Multimodal retinal imaging of diabetic macular edema: toward new paradigms of pathophysiology. *Graefe's Arch. Clin. Exp. Ophthalmol.* **254,** 1661–1668 (2016).
13. Verma, a *et al.* Is neuronal dysfunction an early sign of diabetic retinopathy? Microperimetry and spectral domain optical coherence tomography (SD-OCT) study in individuals with diabetes, but no diabetic retinopathy. *Eye (Lond).* **23,** 1824–30 (2009).
14. Stunf Pukl, S. *et al.* Visual Acuity, Retinal Sensitivity, and Macular Thickness Changes in Diabetic Patients without Diabetic Retinopathy after Cataract Surgery. *J. Diabetes Res.* **2017,** 3459156 (2017).
15. Vujosevic, S. *et al.* Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. *Retina* **30,** 908–16 (2010).
16. Luttrull, J. K. & Dorin, G. Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review. *Curr. Diabetes Rev.* **8,** 274–84 (2012).
17. Brader, H. S. & Young, L. H. Y. Subthreshold Diode Micropulse Laser: A Review. *Semin. Ophthalmol.* **31,** 30–9 (2016).
18. Inagaki, K., Ohkoshi, K. & Ohde, S. Spectral-domain optical coherence tomography imaging of retinal changes after conventional multicolor laser, subthreshold micropulse diode laser, or pattern scanning laser therapy in Japanese with macular edema. *Retina* **32,** 1592–600 (2012).
19. Luttrull, J. K. Low-intensity/high-density subthreshold diode micropulse laser for central serous chorioretinopathy. *Retina* 1658–1663 (2016). doi:10.1097/IAE.0000000000001005
20. Luttrull, J. K. & Sinclair, S. H. Safety of Transfoveal Subthreshold Diode Micropulse Laser for Fovea-Involving Diabetic Macular Edema in Eyes With Good Visual Acuity. *Retina* **34,** 2010–2020 (2014).
21. Peracha, Z.H & Rosenfeld, PJ. Managing DME During Pregnancy. *Retina Specialist*. 11-12 (Nov 2015).