Title of research study: *microPUlse Laser for Suppression of diabetic macular Edema (PULSE Study)*

Investigator: Glenn Yiu, MD, PhD

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you have been diagnosed with Diabetic Macular Edema (DME). The purpose of this study is to determine if early intervention with micropulse laser treatment in eyes with good visual acuity (20/32 or better) will improve or stabilize vision loss due to the complications of diabetic macular edema.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at (916) 734-6303.

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to the Ophthalmology Physician on-call. In the case of an emergency, dial 911 from any phone.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-

admin/.You may talk to an IRB staff member at (916) 703-9151, hs-irbadmin@ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

Diabetic macular edema (DME) is the term used for swelling in the central part of the retina. The retina is the light-sensitive tissue which lines the back of the eye and is responsible for sharp, straight-ahead vision. The retina is nourished by blood vessels. These blood vessels can become weakened by diabetes; causing the retina to become thickened or swollen. Swelling of the central part of the retina can cause vision loss.

Some common treatment strategies for vision loss due to diabetic macular edema are laser treatment, or intra-ocular injections with medications such as corticosteroids or anti-vascular endothelial growth factor (anti-VEGF).

The purpose of this study is to test the effect of early treatment using the subthreshold micropulse diode laser (SML), a laser treatment that delivers laser energy in a "chopped" fashion allowing the tissue being treated to cool between pulses. Previous studies have shown that early intervention with subthreshold micropulse laser (SML) may significantly improve or stabilize vision loss.

How long will the research last?

We expect that you will be in this research study for two years.

How many people will be studied?

We expect to enroll 36 eyes (both eyes will be evaluated for eligibility)

What happens if I say yes, I want to be in this research?

If you choose to participate, and meet the study eligibility criteria, you will be asked to sign this consent form.

On the day you sign the consent (baseline visit), you will be randomly assigned to receive either subthreshold micropulse laser treatment or a sham treatment. A sham treatment is designed to resemble a real laser treatment. The sham procedure is used so that you will not be able to tell if you are receiving the laser treatment or control/observational treatment.

The treatment you get will be chosen by chance, like flipping a coin. You will have a higher chance of being assigned to the laser treatment group than the sham treatment group (2:1 ratio). 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.

- Treatment Group: Subthreshold Micropulse Laser (SML)

  If you are randomized into the treatment group, you will undergo the laser procedure in the outpatient clinic. This procedure will involve sitting in front of a slit lamp and looking into a light. A numbing gel will be placed in your eye prior to the laser procedure. Your eye will be held open using a macula lense. This procedure will take approximately 15 minutes to complete. You should not feel any pain, but may experience some blurry vision for several hours after the procedure.

- Sham Treatment Group:

  Those in the sham treatment arm will not undergo any laser treatment. You will be asked to sit in front of a slit lamp and look into a light. A numbing gel will be placed in your eye. Your eye will be held open using a macula lense. This procedure will take approximately 15 minutes to complete. You should not feel any pain, but may experience some blurry vision for several hours after the procedure.

Study Procedures

The study involves 10 scheduled study visits; baseline (day of enrollment), followed by 1, 3, 6, 9, 12, 15, 18, 21 and 24 months after the day of enrollment.

Each study visits will include the following procedures:

- Measurement of your best-corrected visual acuity(the ability to read letters on the vision chart); low luminance visual acuity (the ability to read letters on the vision chart using a dark filter to reduce the lighting); and contrast sensitivity (the ability to read letters on the vision chart in shades of grey).
- Intraocular pressure measurement: This is a test to measure the pressure inside your eye and is routinely done as part of most eye exams. Eye drops to numb your eyes will be placed in your eyes. The study doctor or staff will touch an instrument to your eyes to measure the pressure inside your eyes.
- Complete eye examination: The structures inside the eye will be examined through a special microscope (slit lamp). The back of the eye will also be examined with an ophthalmoscope (an instrument with a strong light and magnifying lens). Your study doctor may use dilating drops in your eyes to widen your pupils.
- SD-OCT (Spectral Domain- Optical Coherence Tomography): A measurement of the thickness of your retina. This is a non-contact, non-invasive imaging technique that uses light to view the retina (back of the eye).
- Fundus Autofluorescence (FAF): A non-invasive procedure which uses the fluorescent properties of pigments in the retina to create a black and white image.
- Microperimetry: A procedure similar to visual fields (you press a trigger each time you perceive a light stimulus) this examination measures your visual perimetry field with an added camera feature to track eye movement and ensure fixation stability. As you perceive the light stimulus,

you will 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.

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.

If vision declines to 20/40 or worse at any study visit, patients in the treatment arm will undergo repeat SML laser while those in the sham arm will undergo repeat sham laser.

For all study patients - If at any point your vision becomes 20/40 or worse, you will be asked to return to the clinic within 28 days in order to confirm your 20/40 vision. If you are still 20/40 or worse after this repeat visit, you will have reached the study endpoint. After the study endpoint is reached, you will continue your follow up with your doctor as needed. You may be treated on a monthly, as needed, or "treat-and-extend" basis based on the individual investigator's preference. You will then be given any combination of intravitreal anti-VEGF injection, laser, or steroid injection, based on the discretion of the study doctor. All information from these visits will be documented for the study until the end of your 24 month enrollment.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be asked to come to your scheduled visits. If you cannot attend an appointment, please contact study personnel as soon as possible. You will be asked to report any changes in your vision or changes in your health.

What happens if I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you.

Instead of being in this research study, you may continue to be monitored by your doctor.

What happens if I say yes, but I change my mind later?

You can leave the research at any time and it will not be held against you.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care; if you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?

Eye Dilation Drops

During an eye examination, drops may be used to widen the pupils of your eyes. These may cause brief stinging when they are first placed in your eyes. Widened pupils may cause you to be sensitive to light and experience some blurring of your eyesight, especially up close. The effects of the drops may take several hours to wear off. It is recommended that you do not drive until the effects of the drops wear off.

Eye Examinations and Photographs
You may feel temporary discomfort during the eye examinations and photographs due to the bright lights. When the study doctor is examining the back of your eye, he/she will sometimes need to put mild pressure on your eye (through the eyelid). This causes mild to moderate, momentary discomfort.

Spectral Domain Optical Coherence Tomography (OCT)
The Spectral Domain optical coherence tomography measures the thickness of the back of the eye using a very low power laser. There is minimal discomfort due to the light. No other risks are associated with this test.

Subthreshold Micropulse Laser (SML)
Micropulse laser involves applying a very low amount of laser energy in a "chopped" fashion; past animal and human studies have shown that SML does not lead to any detectable damage to the retina. There may be some temporary decrease in vision on the day of the treatment, mostly due to the light used to see the retina when the laser is performed, rather than the laser treatment itself. While the risks associated with traditional "continuous wave" laser include vision loss, visual blind spots, distortion, or abnormal blood vessel formation in the eye; these risks are not associated with micropulse laser treatment.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include improvement or stabilization of your vision. Your participation may help others with Diabetic Macular Edema (DME) as a result of the knowledge gained from this research for future treatments.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB and other University of California representatives responsible for the management or oversight of this study.

The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission. Your medical records may become part of the research record. If that happens, your research records may be looked at by the sponsor of this study and government

agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

If you agree to participate in this research study, a signed copy of this consent document and the privacy authorization form may be filed in your electronic medical record (EMR) and your study participation may be added to your EMR. This information will be used for your care and treatment and for healthcare operations, which may include billing and payment. Federal and state privacy laws give patients the right to access information about their care and treatment contained in their medical record. During this study, you may not be able to access certain information related to this study in your EMR until the study is complete to ensure that the study remains unbiased. If necessary for your care, this information will be provided to you or your physician.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/legal/privacy/) and in an attached document.

What else do I need to know?

This research is being partially funded by Iridex, also called the sponsor. Sponsors may change or be added.

Principal Investigator, Glenn Yiu, MD, PhD received payment from the sponsor for participating in an Opinion Leader interview on behalf of Iridex, the study sponsor.

You or your health plan will be billed for the costs of routine medical care you receive during the study (routine medical care is the care you would have received regardless of your decision to participate in this study). These costs may include eye exams, imaging fees, laser treatment, etc. Only those procedures that are not considered "standard of care" (for example exams performed more frequently than considered necessary to adequately monitor your condition) will be covered by the department or the sponsor. You will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered. For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

You will not be compensated for taking part in this study.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at HS-IRBAdmin@ucdavis.edu.

Do not write below this line. For IRB stamp and version date only.

10Mar2021

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

[Add the following block if a witness will observe the consent process. E.g., short form of consent documentation or illiterate subjects.]

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	Date
Printed name of person witnessing consent process	

Do not write below this line. For IRB stamp and version date only.

10Mar2021