VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	INflammatory MediatorS in the Pathophyslology of Diabetic REtinopathy (INSPIRE) Study – DIABETIC GROUP
Version Date:	04/NOV/2022
PI:	Stephen Kim, MD

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
You are being asked to take part in this research study because nearly 300 million individuals have diabetes worldwide and the prevalence is rising. Over one-third of diabetic patients will develop diabetic retinopathy (DR). Five to 10% of these individuals will suffer from vision-threatening complications. DR progresses in many patients despite preventable measures such as blood sugar and blood pressure control. DR remains the leading cause of legal blindness among working-age adults. Current diagnostic tests fail to identify early disease stages or predict disease progression. Consequently, new biomarkers and therapeutic strategies are needed.

We will enroll 200 adult type II diabetic patients, aged 18 years or greater. We will also enroll 100 age-matched patients without diabetes who are undergoing unilateral vitrectomy surgery for non-inflammatory conditions such as epiretinal membrane or macular hole. Removed aqueous fluid that is typically discarded will instead be collected and stored. Aqueous fluid will be tested for inflammatory markers to provide a reference level for cross-comparison analysis.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be

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told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

You will be questioned about side effects at each study visit. Topical ketorolac (Acuvail PF 0.45%) has the greatest body of literature affirming its safety and has been used chronically (off-label) for years in many patients, but rare associations with corneal melting have been reported. Additional side effects are also rare but can occur, these include:

- 1% to 6%: Ophthalmic: Burning sensation of eyes (transient; Acuvail PF 0.45%: 1% to 6%). Central nervous system: Headache (1% to 6%). Hypersensitivity: Hypersensitivity reaction (over-reaction to light).
  Ophthalmic: Blurred vision (1% to 6%), conjunctival hyperemia (redness of the white area of the eye)(1% to 6%), corneal edema (swelling of the clear area of the eye) (1% to 6%), eye pain (1% to 6%), increased intraocular pressure (increased pressure in your eyes) (1% to 6%), lacrimation or tearing (more than normal watering of the eye) (1% to 6%), corneal infiltrates (small hazy grey areas on the clear part of the eye) (1% to 5%), ocular edema (eye swelling) (1% to 5%), eye irritation, iritis (inflammation of the colored area of the eyes), ophthalmic inflammation (eye immune reaction), superficial keratitis (inflammation of the clear area of the eye), superficial eye infection

A safety monitoring committee, including cornea expert, will review any adverse events.

Aqueous biopsies are performed routinely and are generally considered minor procedures. Risk of bleeding and infection can occur but are rare. The principle investigator and co-investigator Dr. Sapna Gangaputra are well experienced in this procedure having performed over 1000 of them collectively in the standard care of patients with retinal disease and ocular inflammation.All topical NSAIDS used in this study are FDA-approved.

This study will be capturing some information about you that includes identifiable, personal information, like your date of birth. The study has procedures in place to protect that information. There is a chance that a loss of that protection could occur. This would be a loss of confidentiality. Please see the "Confidentiality" section below for more information.

Risks that are not known:

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Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. The following risks may include: the fluorescein corneal staining test may be uncomfortable if your eyes are very dry, the blotting paper feels scratchy as it touches your eyes, and the dye could sting a little bit or slightly stain your skin, but those will go away quickly. Your doctor may use numbing drops to make the test more comfortable. Other risks include an allergenic reaction if you are allergic to fluorescein (dye) or proparacaine (numbing drop).

Good effects that might result from this study:
The benefits to science and humankind that might result from this study:

- Delayed onset and progression of Diabetic Retinopathy and Diabetic Macular Edema

Procedures to be followed:

You will undergo a complete baseline ophthalmic examination of both eyes including best corrected visual acuity (how well your eyes can see with corrective lenses, if needed, intraocular pressure (IOP) measurement (measure of the pressure inside the eye using numbing drops and a special device that gently touching the front surface of the eye), slit-lamp examination (the doctor will take a close look at your eye with a bright light and a special microscope, dilated funduscopic examination (eye drops will be placed inside both eyes to enlarge the pupil and the doctor will look at the inside back surface, or retina, of your eye with a bright light and a special lens), Spectral Domain Optical Coherence Tomography (SDOCT: a certified ophthalmic photography technician will obtain sub-surface images of the inside back surface, or retina, of your eye at a resolution equivalent to a low-power microscope. It is effectively 'optical ultrasound', imaging reflections from within tissue to provide cross-sectional images, optical coherence tomography angiography (OCTA: similar to SDOCT that will be used to help assess the health of the blood vessels in the back of the eye), Schirmer's testing (your eyes will be numbed with a drop, and a strip of paper will be placed in the lower eyelid to collect tears in order to determine how well your eyes are producing tears, Optos (Optomap Retinal Exam) color fundus photography of the macula and 7-field photography of the peripheral retina (color photographs will be taken of the inside back surface, or retina, of your eye), as well as specular microscopy (magnified reflected light images of the cell layer of the back surface of the clear front layer of the eye, or cornea, to help determine the corneal health) . You will have serum blood glucose and HbA1c tested and will undergo bilateral aqueous fluid biopsies at baseline. The aqueous fluid biopsy tap will occur in clinic with all aseptic precautions. The aqueous fluid is the fluid inside the eye that is constantly being produced and drained within the eye itself and occupies the front chamber of the eye from the cornea (the front clear covering of the eye) to immediately behind the pupil and around the lens. This area of the eye is also called the anterior chamber. During the biopsy/tap procedure your eye will be numbed with a numbing drop and sterilized

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with an antibiotic drop. The doctor will then remove a very small amount of aqueous fluid from the anterior chamber of the eye with a small needle and syringe through the cornea, or clear part of the eye. This aqueous humor sample will be stored in Dr. Kim's lab. At the baseline visit, if you are in the moderate NPDR group, you will be randomized, like flipping a coin, into either the active treatment group (Acuvail PF) or the placebo-control (preservative-free artificial tears) group.

If you are randomized to either Acuvail or placebo-control (preservative-free artificial tear) you will be instructed to apply 1 drop of study or control medication 2 times daily in your eyes and then to close them for 5 minutes to improve absorption. The Investigational Drug Service at Vanderbilt will obtain study drugs and dispense them to patients at each visit. You will continue treatment for 3 years, the duration of the study.
Physicians, patients, coordinators and research assistants are masked to the content of the drops and they will be dispensed in similar appearing bottles with similar consistency and appearance of the drops, so neither you, Dr. Kim or any of his study staff will know if you are receiving Acuvail or artificial tears

You will follow with Dr Kim and Dr Gangaputra every 4 months for 3 years. At each follow up visit, you will undergo a full exam to evaluate for any AE's and repeat all testing that was done at baseline - best corrected visual acuity, intraocular pressure (IOP) measurement, slit-lamp examination, dilated funduscopic examination, SDOCT, optical coherence tomography angiography (OCTA), Schirmer's testing, color fundus photography of the macula and 7-field photography of the peripheral retina, as well as specular microscopy, serum blood glucose, HbA1c and bilateral aqueous biopsies.

You will have a yellow dye added to the eye to complete an oxford grading cornea scale at each visit; graded from severity 0 (absent) to 5 (severe) for dry eye. If a grade 1-2, you will be advised to use more lubrication, if grade 3 or higher, you will be sent to a cornea evaluation (dry eye specialist). An ocular surface disease index (OSDI) questionnaire will be performed by you yearly for dry eye.

The purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood for genetic research. What we learn about you from this sample will not be put in your health record. No one else (like a relative, boss, or insurance company) will be given your test results.

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A single blood sample will be drawn from a vein in your arm using a needle. This will take about 15 minutes of your time. You may feel bothered or pained from the needle stick. You may have a bruise or the site may get infected. It is rare, but some people faint.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

At any time, you may ask to have your sample destroyed. You should contact Dr. Kim at 615-936-2020 2311 Pierce Ave Nashville, TN to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Kim, and the research team will have access to your name.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Your sample will be used to make DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

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Payments for your time spent taking part in this study or expenses:
The study will provide $25 dollar visa check cards to patients to cover their travel cost. Patients will receive a $50 visa check card to compensate for the longer appointment times, or longer travel times. The study will provide compensation for co-pays.

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Stephen Kim at 615-936-2020. If you cannot reach the research staff, please page the study doctor at 615-936-2020

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

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

Confidentiality:

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The investigators/study team will take all appropriate measures to ensure that the anonymity you will be maintained according to Good Clinical Practice (GCP). You will be identified by your patient identification number, only, on case report forms or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed Informed Consent Forms/subject ID log) will be kept in strict confidence and under lock and key in the Clinical Trials Department office. Deidentified OCTA scans will be sent to NYEE for analysis via our secure sFTP (Accelion). The original scans will reside on parent software (Optovue).

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Study Results:
Any information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done. These tests may help us or other researchers learn more about using topical NSAID's for the prevention of DR.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical

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Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Legally Authorized Representative (if applicable):

_____ _____
Date Signature

_____
Relationship to subject

Impartial witness (if applicable):

_____ _____
Date Signature

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There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research in this study.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research in _____.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

Signature: _____ Date: _____