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- (71) Applicant: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 5th Floor, Oakland, California 94607-5200 (US).
- (72) Inventor: **FREEMAN, William R.**; 4752 Vista de la Tierra, Del Mar, California 92014 (US).
- (74) Agents: **MUSICK, Eleanor, M.** et al.; Musick Davison LLP, 12636 High Bluff Drive #400, San Diego, California 92130 (US).

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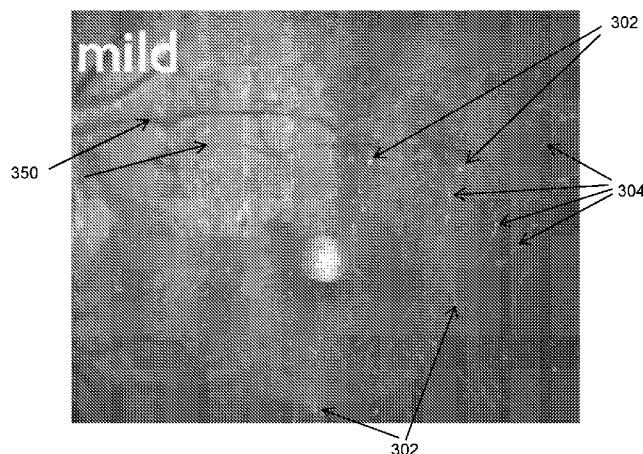


FIG. 7B

(57) Abstract: A scanning laser ophthalmoscope is configured to collect laser light projected onto and reflected from the fundus of the eye of a subject. An image of the reflected light is evaluated for one or more reticular patterns in the cornea as an indicator of the presence of dry eye syndrome. The size, density and number of branches within the reticular pattern(s) are used to generate a score correlated to the severity of the DES symptoms.

METHOD AND SYSTEM FOR OBJECTIVE EVALUATION OF DRY EYE SYNDROME

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RELATED APPLICATIONS

This application claims the benefit of the priority of U.S. Provisional Application No. 62/110,855, filed February 2, 2015, which is incorporated herein by reference in its entirety.

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FIELD OF THE INVENTION

The present invention relates to a system and method for evaluation of dry eye syndrome using scanning laser ophthalmoscopy (SLO).

BACKGROUND OF THE INVENTION

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Dry eye syndrome (DES) is a multifactorial disease of the tears and the ocular surface that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. DES can be accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Multiple causes can produce either inadequate tear production or abnormal tear film constitution, resulting in excessively fast evaporation or premature destruction of the tear film. DES is a very common in the United States, affecting a significant percentage of the population -- approximately 10-30%, especially those over 40 years old. An estimated 3.23 million women and 1.68 million men aged 50 years and older are affected.

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The visually important area of the cornea is approximately the same diameter as the pupil. The cornea is avascular, with oxygen supply coming mainly from the tear film and metabolic requirements from the aqueous humor. The cornea includes five distinct layers: 1) epithelium, the layer of cells that cover the outer surface of the cornea and comprises about 10 percent of the cornea's total thickness. The epithelium functions primarily to block passage of foreign material into the eye and other layers of the cornea and to provide a smooth surface that absorbs oxygen and cell nutrients from tears; 2) Bowman's layer, a thin, homogeneous, transparent, condensed acellular stroma composed of fine fibers which are tightly connected with the stroma; 3) the stroma, the thickest layer of the cornea representing 90% of total corneal thickness and

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consisting primarily of water (78%) and collagen (16%). The stroma is not renewable if injured; 4) Descemet's membrane, a thin, strong sheet of tissue that serves as a protective barrier against infection and injuries; and 5) endothelium, the extremely thin, innermost layer of the cornea responsible for keeping the cornea clear.

5 In extreme cases, dry eye may be complicated by sterile or infectious corneal ulceration. Occasionally, corneal perforation may occur. In rare cases, sterile or infectious corneal ulceration in dry eye syndrome can cause blindness. Early detection and aggressive treatment of DES may help prevent corneal ulcers, scarring, and possible vision loss. Treatment depends on the level of severity and may include
10 medications, eye protection devices, and surgical interventions. The frequency of follow-up care depends on the severity of the signs and symptoms. Environment-related issues that may exacerbate the DES should be discussed; alternatives may be needed.

 Most patients have mild-to-moderate cases that can be treated symptomatically
15 with lubricants, providing good relief of symptoms. In general, the prognosis for visual acuity in patients with dry eye syndrome is good. Patients with prolonged untreated dry eye represent a subgroup that has a poor prognosis and requires a longer course of treatment. As a consequence of the demographic pressure created by an aging population, DES is expected to increase in prevalence and thus to impose a growing
20 burden on ophthalmologic practices.

 A clinical diagnosis of DES is typically made by combining information obtained from the patient history, physical examination, and one or more tests intended to lend some objectivity to the diagnosis. In every area of medicine, the key characteristics of any effective diagnostic procedure are its measurability and
25 reproducibility. Presently, no single test is sufficiently specific to permit an absolute diagnosis of DES.

 Studies that may be used for DES diagnosis include: impression cytology (monitoring the progression of ocular surface changes); measurement of tear breakup time (TBUT); the Schirmer test; and quantification of tear components. One
30 commercially-available test is InflammDry (Rapid Pathogen Screening, Inc.), which uses tear samples from the patient to detect the inflammatory marker matrix metalloproteinase-9 ("MMP-9"). MMP-9 has been shown to be consistently elevated

in the tears of patients with dry eye disease. A commercially-available MMP-9 test is InflammDry[®] from Rapid Pathogen Screening, Inc., Sarasota, Florida. A possible drawback of this test is that it may be difficult to obtain an adequate tear sample from a patient already suffering from insufficient tear production and it does not directly measure the effect of abnormal tear film and changes in the optical quality of the patient's vision due to dry eye. Additional tests that may be used in a workup include: tear stability analysis system (TSAS); tear function index (TFI; Liverpool modification); and tear ferning test (TFT). None of these are a direct measure of the effect of abnormal tear film stability on the optics of the visual system.

Confocal scanning laser ophthalmoscopy (cSLO) is a method of examination of the eye that uses confocal laser scanning microscopy for diagnostic imaging of the retina or cornea of the human eye. Confocal imaging is the process of scanning an object point-by-point by a focused laser beam using horizontal and vertical scanning mirrors and capturing the reflected light through a small aperture (a confocal pinhole). The confocal pinhole suppresses light reflected or scattered from outside of the focal plane, which otherwise would blur the image. The result is a sharp, high contrast image of the object layer located at the focal plane that is viewable on a television monitor.

Advantages of using cSLO over traditional fundus photography include improved image quality, small depth of focus, suppression of scattered light, patient comfort through less bright light, 3D imaging capability, video capability, and effective imaging of patients who do not dilate well. cSLO is used for fluorescence imaging as well as to generate monochromatic or pseudo color images of the fundus. One commercially available SLO system is the SPECTRALIS[®] platform from Heidelberg Engineering, Inc., which is capable of performing spectral-domain optical coherence tomography (SD-OCT) as well as cSLO. The SPECTRALIS[®] system includes multiple imaging modes for different diagnostic applications. The imaging modes include multicolor imaging using multiple laser colors, infrared reflectance, blue autofluorescence and reflectance, and green fluorescein, all designed to enhance the ability to visualize the fundus.

The need remains for a minimally-invasive test that can be performed quickly to provide an objective evaluation of a patient experiencing symptoms of, or suspected to

be suffering from, DES, and that can rapidly indicate efficacy of treatment. The present invention is directed to such a method.

SUMMARY OF THE INVENTION

In an exemplary embodiment, a scanning laser ophthalmoscope is configured to collect laser light projected onto and reflected from the fundus of the eye of a subject. An image of the reflected light collected by an image detector is evaluated for one or more reticular patterns, which may include circles, spots, lines and/or branches, resulting from apparent variations in transmissivity of the reflected light through the cornea. The appearance of the reticular patterns in the cornea indicates the presence of dry eye syndrome and is a measure of the abnormality of the tear film itself and correlates with symptoms and with visual degradation as it reflects changes of the major reflecting surface of the eye; the anterior surface of the cornea. The reticular pattern increases during imaging, indicating further drying during observation. The size, density and number of branches within the reticular pattern(s) are correlated to the severity of the DES symptoms. Upon application of topical lubricants, the reticular pattern decreases or disappears entirely, with corresponding reduction in DES symptoms as indicated by the subject. In one embodiment, the reticular pattern can be most prominently seen in multicolor images, but is also visible using monochromatic light, particularly blue or green channels.

Both qualitative and quantitative assessment of the severity of a patient's DES condition may be achieved by estimating or counting the number of lines and branches within the reticular pattern. A score may be assigned based on the numbers of lines and branches, by the area covered by the total pattern, or by some combination thereof. In one embodiment, automated detection and scoring of the patient's DES severity, as well as the efficacy of treatment, may be performed by using computer-aided image analysis techniques as are known in the art. Such algorithms may be used to quantify dry eye severity by grading the prominence of the reticular pattern.

In recent years, machine-learning approaches for image analysis have been widely explored for recognizing patterns which, in turn, allow extraction of significant features within an image from a background of irrelevant detail. Image processing techniques for feature extraction are well known in the art and may include Fourier

transform, discrete cosine transform (DCT), wavelet and other transforms, edge detection, segmentation, shape matching, and many other image processing algorithms. Learning machines comprise algorithms that may be trained to generalize using data with known outcomes. Trained learning machine algorithms may then be applied to predict the outcome in cases of unknown outcome. Machine-learning approaches, which include (without limitation) neural networks, hidden Markov models, Bayesian networks classifiers, belief networks and support vector machines, are ideally suited for domains characterized by the existence of large amounts of data, noisy patterns and the absence of general theories. Particular focus among such approaches has been on the application of artificial neural networks to biomedical image analysis, with results reported in the use of neural networks for analyzing visual images of cytology specimens and mammograms for the diagnosis of breast cancer, classification of retinal images of diabetics, karyotyping (visual analysis of chromosome images) for identifying genetic abnormalities, and tumor detection in ultrasound images, among others.

In one aspect of the invention, a method for evaluation of dry eye syndrome in a patient includes detecting a reticular pattern in an image of the patient's cornea generated using light backscattered from the patient's fundus. In some embodiments, the reticular pattern comprises lines and branches. In other embodiments, the method includes detecting an obscuration of retinal structures within the image. The light is preferably one or more light colors selected from multi-color, blue and green.

The method may include the use of a computing device to analyze a digital image to count a quantity of lines and branches, compare the quantity against one or more pre-determined thresholds; and if the quantity exceeds the one or more pre-determined thresholds, assign a score corresponding to an exceeded threshold. The step of counting may include pre-processing the digital image to extract features corresponding to the reticular pattern; and using a trained classifier to classify the reticular pattern based on the extracted features.

In another aspect of the invention, a method for evaluation of dry eye syndrome in a patient includes generating an image of the patient's cornea using a scanning laser ophthalmoscope; detecting a reticular pattern within the image; and grading the reticular pattern according to a pre-determined scale based on a quantity of dots, lines

and branches within the reticular pattern, where the pre-determined scale corresponds to a severity of dry eye syndrome. In a preferred embodiment, the scanning laser ophthalmoscope generates backscatter images using light comprising one or more light colors selected from multi-color, blue and green. In some embodiments, the method
5 further includes detecting an obscuration of retinal structures within the image. The steps of detecting and grading may be executed using a computing device, which may further perform steps for pre-processing the digital image to extract features corresponding to the reticular pattern; and using a trained classifier to classify the reticular pattern based on the extracted features. In a preferred embodiment, the
10 scanning laser ophthalmoscope is a confocal scanning laser ophthalmoscope.

In still another aspect of the invention, a system for evaluation of dry eye syndrome in a patient includes a scanning laser ophthalmoscope configured for generating a backscatter image using light comprising one or more light colors selected from multi-color, blue and green; and a computing device configured for detecting a
15 reticular pattern within the backscatter image; and grading the reticular pattern according to a pre-determined scale based on a quantity of dots, lines and branches within the reticular pattern, wherein the pre-determined scale corresponds to a severity of dry eye syndrome. In some embodiments, the computing device is further configured for pre-processing the backscatter image to extract features corresponding to the
20 reticular pattern; and using a trained classifier to classify the reticular pattern based on the extracted features.

To provide an objective analysis of the severity of DES in a patient, the reticular patterns observed in the images are assigned a score based on a grading scale in which alphanumerical values correspond to the degree or quantity of reflections
25 within a pattern. For example, a four level scale could include a lowest level, e.g., “0”, corresponding to no abnormal reflections. The next lowest level, “1”, would correspond to mild reticular reflections; “2” for moderate reticular reflections; and “3” for several reticular reflections. Alternative label formats may be used, including descriptive terms or other alphanumeric characters used to distinguish among the different levels.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagrammatic view of the basic components of an exemplary scanning laser ophthalmoscope.

FIG. 2 is a diagrammatic view of an embodiment of an exemplary SLO.

5 FIG. 3 is a block diagram of an exemplary automated DES evaluation.

FIGs. 4A and 4B are retinal photographs taken for different patients using an exemplary SLO with multicolor laser light showing varying degrees of DES as indicated by the presence of reticular patterns.

10 FIGs. 5A and 5B are retinal photographs taken for different patients using an exemplary SLO with green laser light showing varying degrees of DES as indicated by the presence of reticular patterns.

FIGs. 6A and 6B are retinal photographs taken for different patients using an exemplary SLO with blue laser light showing varying degrees of DES as indicated by the presence of reticular patterns.

15 FIGs. 7A-7D are retinal photographs taken for patient's exhibiting levels of DES graded as normal, mild, moderate and severe, respectively.

DETAILED DESCRIPTION

According to the present invention, a scanning laser system is used to evaluate patients with dry eye syndrome by observing a specific pattern that appears to emanate from the cornea, which dries further during imaging and causes a reticular or reticular-with-circle pattern. This pattern is most prominently seen in multicolor images, and is also easily visualized using individual blue and green channels. The pattern goes away when frequent topical lubricants are used during imaging, providing an indicator of therapeutic efficacy.

25 Scanning laser ophthalmoscopy (SLO) is a method of examination of the eye that uses confocal laser scanning microscopy for diagnostic imaging of retina or cornea of the human eye. Confocal imaging is the process of scanning an object point by point by a focused laser beam using horizontal and vertical scanning mirrors and capturing the reflected light through a small aperture (a confocal pinhole). The confocal pinhole
30 suppresses light reflected or scattered from outside of the focal plane, which otherwise

would blur the image. The result is a sharp, high contrast image of the object layer located at the focal plane that is viewable on a television monitor.

In an exemplary embodiment, a scanning laser ophthalmoscope is configured to collect laser light projected onto and reflected from the fundus of the eye of a subject.

5 An image of the reflected light collected by an image detector is evaluated for one or more reticular patterns, which may include circles, spots, lines and/or branches, resulting from apparent variations in transmissivity of the reflected light through the cornea. The appearance of the reticular patterns in the cornea indicates the presence of dry eye syndrome and reflects optical changes in the anterior refracting surface of the

10 eye due to drying and instability of the tear film. The reticular pattern increases during imaging, indicating further drying during observation. The size, density and number of branches within the reticular pattern(s) are correlated to the severity of the DES symptoms. Upon application of topical lubricants, the reticular pattern decreases or disappears entirely, with corresponding reduction in DES symptoms as indicated by the

15 subject.

In one embodiment, the reticular pattern is most prominently seen in multicolor images, but is also visible using monochromatic light, specifically blue or green channels.

Both qualitative and quantitative assessment of the severity of a patient's DES

20 condition may be achieved by estimating or counting the number of lines and branches within the reticular pattern. A score may be assigned based on the numbers of lines and branches, by the area covered by the total pattern, or by some combination thereof. In one embodiment, automated detection and scoring of the patient's DES severity, as well as the efficacy of treatment, may be performed by using computer-aided image

25 analysis techniques as are known in the art.

The following description relates to a generic SLO system that may be adapted for use in an objective evaluation of DES, but is not intended to be limiting with respect to any specific structure of elements required to implement the inventive method. FIG. 1 illustrates the basic components of an exemplary scanning laser

30 ophthalmoscope 10, while FIG. 2 provides additional detail for an exemplary SLO system. Referring first to FIG. 1, SLO 10 includes a laser light source 70 that projects beams of different wavelengths through imaging optics 32 toward the patient's eye 12

and the retina 68. Light is reflected from the retina back through the imaging optics 32, through confocal aperture 36 for detection by detector 118.

Referring now to FIG. 2, the illumination system 30 includes a laser source 70 generates a laser beam 72 that impinges on a passive, stationary optical element 74 at a point. The passive, stationary optical element 74, which may be a cylindrical lens as shown, generates a line of light from the point of light impinging on the lens 74. The line of laser light is scanned in a direction perpendicular to the direction of the line 76 by a scanner mirror 78 on which the line of light impinges, the scanner mirror 78 being driven by a scanner motor that is coupled to the mirror 78. As the scanner mirror 78 vibrates, it scans the line horizontally across the face of the partially reflective beam splitter 40 so that a rectangular shaped area of illumination is generated on the face of the beam splitter 40. The beam splitter 40 reflects the rectangular area of illumination light towards the eye 12 so that it is centered on the real image plane 58 and aspheric lens 60. The illumination light continues its path until it strikes the retina.

In order to generate a color image of the interior of the patient's eye 12 at varying depths therein, the laser source 70 includes a number of lasers each of which produces a laser beam of a different wavelength, preferably associated with blue (λ_B), green (λ_G) and red (λ_R) laser light. For multi-color scanning, the laser light of different wavelengths generated by the lasers within source 70 may be combined to form a single laser beam 72 by a number of dichroic mirrors. For single color scanning, the lasers may be activated separately. As the laser beam 72 is scanned onto the patient's eye 12, as is well known, different parts of the eye at different depths therein respond to different wavelengths of laser light by reflecting laser light of a particular wavelength.

In order to capture and detect a color image of the interior of the patient's eye 12 at varying depths therein, the eye image capturing and detection system 32 includes the moveable field lens 34. More particularly, as shown in FIGS. 2, an illuminated point on the fundus 66 of the patient's eye 12 reflects light wherein the reflected light is captured and focused by the aspheric lens 60 to a point on the image plane 58. The light reflected from the patient's eye passes through the beam splitter 40 to the mirror 42 that reflects the light from the patient's eye 12 to the moveable field lens 34 of the eye image capturing and detection system 32. The light reflected from the patient's eye

passes through the field lens **34** and from there through a polarizer film **112** into focusing optics including lenses **114** and **116**, through aperture **36**, to impinge on detector **118**, which may be a charge coupled device (CCD), CMOS detector, or other appropriate image detector. The resulting signal corresponding to the image detected
5 by detector **118** is transmitted (via wired or wireless connection) to a computing device **120** for output to a monitor, graphical user interface (GUI), or other appropriate output device, such as a printer. In some embodiments, the image data may be communicated from the computing device **120** to an internal or external storage device, e.g., a database for secure patient data storage, or to some other computer-readable storage
10 medium. In addition, the data may be transmitted via wired or wireless connection or to a tablet, smart phone or other display device for review by a physician or laboratory personnel for evaluation.

In recent years, machine-learning approaches for image analysis have been widely explored for recognizing patterns, which, in turn, allow extraction of significant
15 features within an image from a background of irrelevant detail. Learning machines comprise algorithms that may be trained to generalize using data with known outcomes. Trained learning machine algorithms may then be applied to predict the outcome in cases of unknown outcome. Machine-learning approaches, which include, without limitation, neural networks, hidden Markov models, random forests, Bayesian
20 networks, belief networks, support vector machines and other kernel-based machines, as well as ensemble classifiers that include multiple classifier types, are ideally suited for domains characterized by the existence of large amounts of data, noisy patterns and the absence of general theories. Particular focus among such approaches has been on the application of artificial neural networks to biomedical image analysis, with results
25 reported in the use of neural networks for analyzing visual images of cytology specimens and mammograms for the diagnosis of breast cancer, classification of retinal images of diabetics, karyotyping (visual analysis of chromosome images) for identifying genetic abnormalities, and tumor detection in ultrasound images, among others. In some embodiments of the invention, computing device **120** may optionally
30 include software and/or firmware modules for executing pre-processing algorithms (module **130**) for feature extraction from the images, classification (module **132**), and post-processing (module **134**) of the images to generate a grade or score. Embodiments

incorporating computer-based image analysis may be used as a standalone diagnostic system, as a screening tool to identify images that should be forwarded to an expert, e.g., ophthalmologist, for evaluation to confirm a preliminary machine-based diagnosis/grading, or as a second opinion to verify a technician's screening result.

5 FIG. 3 provides a basic process flow for an automated diagnostic procedure for objective evaluation of DES in a patient. In step **200**, a SLO or similar system is used to perform a laser scan of the patient's eye. This scan may be performed using multicolor, monochromatic, e.g., blue or green, laser light, or a combination of multiple colors and/or multiple scans. The objective lens used to collect the reflected light is
10 preferably a wide-angle lens. While a typical SLO scan may be performed after chemically dilating the patient's pupil, in a preferred embodiment, the scanning procedure may be done in a darkened environment, in which the pupil would naturally dilate, using infrared light to illuminate the fundus. In step **202**, a digital image generated by the scanning system's detector would be input into a computer processor
15 for analysis. In an exemplary processing sequence, in step **204**, the image may then be pre-processed to sharpen the image, enhance contrast, and/or to remove noise or artifacts generated during the scanning process. After pre-processing, the image may be processed in step **206** using known feature extraction techniques including segmentation, edge detection and various transforms to identify recognizable
20 characteristics of the reticular patterns. After extraction of the recognizable features, the features may be classified and/or counted (step **208**). Exemplary classification algorithms suitable for use in such a system include, but are not limited to, support vector machines, neural networks, random forests, Bayesian classifiers and other statistics-based methods. A predetermined threshold or scale, which would preferably
25 be established based on expert knowledge and clinical observation, is then used in step **210** as a basis for scoring the results. The system's output may be a grade or score corresponding to the severity of the patient's DES.

 The correlation between the appearance and complexity of the reticular pattern and the severity of the DES symptoms has been validated by reviewing images from
30 over 70 human eyes. FIGs. **4A** and **4B** are retinal photographs taken using an exemplary SLO with multicolor laser light showing varying degrees of DES as indicated by the presence of reticular patterns. FIGs. **5A** and **5B** are retinal

photographs taken using an exemplary SLO with green laser light showing varying degrees of DES as indicated by the presence of reticular patterns. FIGs. 6A and 6B are retinal photographs taken using an exemplary SLO with blue laser light showing varying degrees of DES as indicated by the presence of reticular patterns.

5 Example 1: Validation of Method in 26 Patients

Fifty-one (51) eyes of twenty-six (26) patients were randomly selected from a schedule list of patients coming in for fluorescein angiography and ocular coherence tomography for retina related diseases. The patients' eyes were scanned using the Heidelberg SPECTRALIS® SLO at the University of California, San Diego Jacobs
10 Retina Center. Dry eye was evaluated by three clinical parameters and three SLO image-related parameters. Tear break up time (TBUT) was measured using fluorescein-impregnated strip placed in the patients' lower conjunctival sac after wetting with non-preserved saline solution. The patient was then asked to blink three to five times and keep their eyes open. The time between the last blink and the appearance
15 of the first dark spot was recorded as TBUT, and graded as <10 seconds or ≥ 10 seconds). Corneal staining was measured after application of fluorescein stain for TBUT measurement. The upper eyelid was lifted slightly to examine the entire cornea for staining that is represented by punctate dots along the surface of the cornea, and graded as no corneal staining or with corneal staining. Meibomian gland grading (using
20 the Tear Film and Ocular Surface Society (TFOS) International Workshop on Meibomian Gland Dysfunction grading scale) was evaluated before dilation by masked examiners. On the same visit day, multicolor (combination of 486 nm, 518 nm and 815 nm wavelengths), blue reflectance (486 nm wavelength) and green reflectance (518 nm wavelength) images using the Heidelberg Spectralis® SLO were taken. Presence of
25 corneal reticulations noted in any of the imaging modalities as evaluated by three observers separately and dry eye as dictated by the three parameters were then evaluated using Pearson Correlation Coefficient test.

Grading system: Since this is a novel finding, it was necessary to create a grading scale for the observers to serve as an objective basis for grading. The grading
30 of the reticular pattern was on a four-level scale: "NORMAL", "MILD", "MODERATE" and "SEVERE." As will be readily apparent to those in the art,

alphanumeric scores or grades may also be applied, e.g., “A” to “D”, “I” to “IV”, etc. and more or fewer levels may be used.

Referring to FIGs. **7A-7D**, the first level, “NORMAL” (FIG. **7A**), exhibited no abnormal reflections, with all retinal structures **350** clearly visible. A “MILD” grade (FIG. **7B**) was given for mild reticular reflections, where dots and specks **302** appeared with connecting lines forming spider web-like structures **304**; retinal structures **350** could still be appreciated. A “MODERATE” grade (FIG. **7C**) was assigned for moderate reticular reflections with the spider web structures of the previous grade were observed along with a faint veil **306** and partial obscuration of the retinal structures **350**. A “SEVERE” grade (FIG. **7D**) was given for severe reticular reflections exhibiting all of the features of the lower grades along with an iridescent veil **308** and significant obscuration of retinal structures.

Corneal reticular pattern was graded separately for each of the wavelengths described above: multicolor, blue and green. Three observers conducted evaluations separately, and inter-observer agreement analysis was performed. The observers were masked to the patient history and the dry eye testing results such as TBUT, corneal staining and Meibomian gland dysfunction grading.

Statistics: We used Kolmogorov-Smirnow, Cramer-von-Mises, and Anderson-Darling tests to evaluate normality. Pearson correlation coefficient was used to evaluate group wise correlation, and ANOVA was used to evaluate the correlation between the three dependent variables (tear breakup time, cornea staining, and Meibomian gland grading) and the image related parameter (presence of reticulations on multicolor, green reflectance, and blue reflectance images).

Results: Of the 26 patients included in this study, fifty (50%) percent were female. The mean age was 78 ± 9.0 years old (57-91). None of the clinical parameters of tear breakup time (TBUT), corneal staining (K staining), and Meibomian gland grading (MGD) were normally distributed. The three image-related parameters were also not normally distributed. This is not surprising, as the observations are categorical parameter. The strongest predictor for reduced tear breakup time and presence of corneal staining was presence of reticulation in multicolor imaging (MC) (p value < 0.0001 with TBUT and p-value 0.0007 with corneal staining). Presence of reticulation on green reflectance (GR) also had significant correlation (p-value < 0.0001 with TBUT

and p-value 0.0047 with corneal staining (K-staining). Blue reflectance (BR) had the least correlation (p-value 0.0029 with TBUT and 0.0715 with corneal staining, not significant). This suggests the reticular SLO pattern seen in MC, GR and BR correlates with ocular surface abnormalities and rapid tear film evaporation in dry eye. There was a negative association between the three imaging modalities and Meibomian gland grading (MGD), as shown in Table 1 below.

	MC	GR	BR
TBUT	0.42431 <.0001	0.41450 <.0001	0.23887 0.0029
K staining	0.27170 0.0007	0.22715 0.0047	0.14611 0.0715
MGD	-0.01664 0.8383	-0.02239 0.7835	-0.02306 0.7772

TABLE 1

Although the role of the Meibomian gland in preventing tear film evaporation is known and is likely due to lipid secretion Meibomian gland dysfunction's effect on tear film integrity is difficult to precisely ascertain. We note that the Tear Film and Ocular Surface Society (TFOS) International Workshop on Meibomian Gland Dysfunction grading scale that we used in this study is somewhat subjective and that this grading scale does not evaluate directly the quality of the tear films' lipid layer.

The methods described herein provide means for both qualitative and quantitative assessment of the severity of a patient's DES condition by grading the prominence of a reticular pattern observed during a SLO scan and estimating or counting the number of lines and branches within the reticular pattern. A score may be assigned based on the numbers of lines and branches, by the area covered by the total pattern, by the level of obscuration of the retinal structures, or by some combination thereof. In some embodiments, automated detection and scoring of the patient's DES severity, as well as the efficacy of treatment, may be performed by using computer-aided image analysis techniques as are known in the art.

CLAIMS:

1. A method for evaluation of dry eye syndrome in a patient, comprising detecting a reticular pattern in an image of the patient's cornea generated using light backscattered from the patient's fundus.
- 5 2. The method of claim 1, wherein the reticular pattern comprises lines and branches.
3. The method of claim 1, wherein the light comprises one or more light colors selected from multi-color, blue and green.
4. The method of claim 1, further comprising detecting an obscuration of
10 retinal structures within the image.
5. The method of claim 2, wherein the image is a digital image and further comprising:
 executing within a computing device the steps of:
 counting a quantity of lines and branches;
15 comparing the quantity against one or more pre-determined thresholds;
 and
 if the quantity exceeds the one or more pre-determined thresholds,
 assigning a score corresponding to an exceeded threshold.
6. The method of claim 5, wherein the step of counting comprises:
20 pre-processing the digital image to extract features corresponding to the
 reticular pattern; and
 using a trained classifier to classify the reticular pattern based on the extracted
 features.
7. A method for evaluation of dry eye syndrome in a patient, comprising:
25 generating an image of the patient's cornea using a scanning laser
 ophthalmoscope;
 detecting a reticular pattern within the image; and
 grading the reticular pattern according to a pre-determined scale based on a
 quantity of dots, lines and branches within the reticular pattern, wherein the pre-
30 determined scale corresponds to a severity of dry eye syndrome.

8. The method of claim 7, wherein the scanning laser ophthalmoscope generates backscatter images using light comprising one or more light colors selected from multi-color, blue and green.

9. The method of claim 7, further comprising detecting an obscuration of retinal structures within the image.

10. The method of claim 7, wherein the image is a digital image and further comprising:

executing the steps of detecting and grading using a computing device.

11. The method of claim 10, wherein the step of detecting comprises: pre-processing the digital image to extract features corresponding to the reticular pattern; and

using a trained classifier to classify the reticular pattern based on the extracted features.

12. The method of claim 7, wherein the scanning laser ophthalmoscope is a confocal scanning laser ophthalmoscope.

13. A system for evaluation of dry eye syndrome in a patient, comprising:

scanning laser ophthalmoscope configured for generating a backscatter image using light comprising one or more light colors selected from multi-color, blue and green; and

a computing device configured for:

detecting a reticular pattern within the backscatter image; and

grading the reticular pattern according to a pre-determined scale based on a quantity of dots, lines and branches within the reticular pattern, wherein the pre-determined scale corresponds to a severity of dry eye syndrome.

14. The system of claim 13, wherein the computing device is further configured for:

pre-processing the backscatter image to extract features corresponding to the reticular pattern; and

using a trained classifier to classify the reticular pattern based on the extracted features.

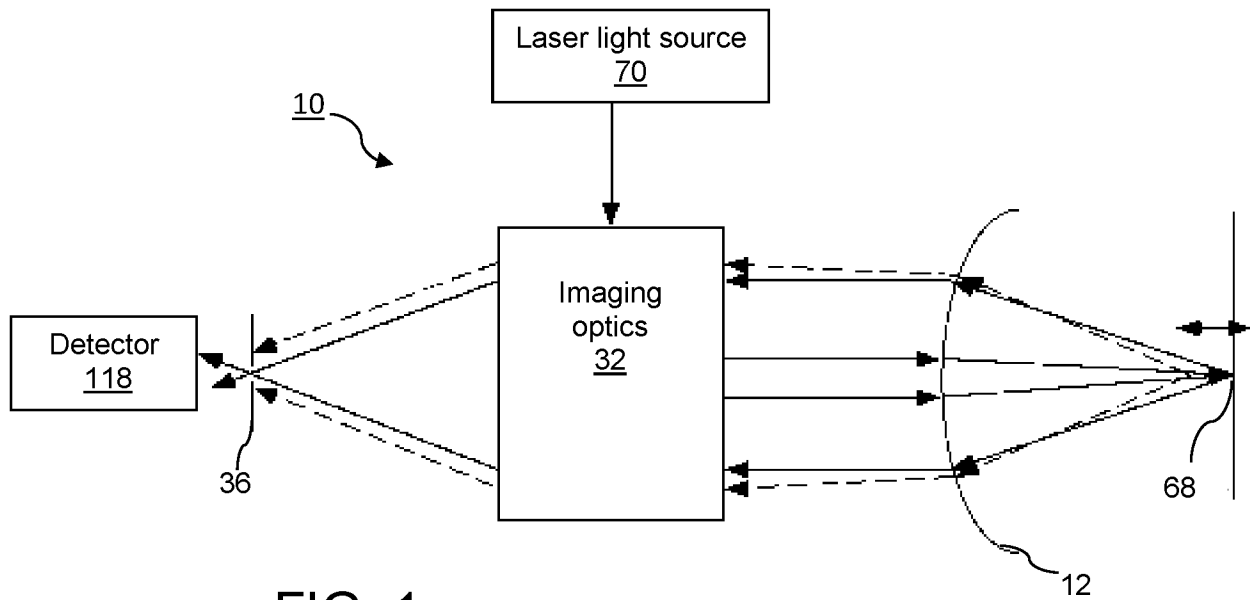
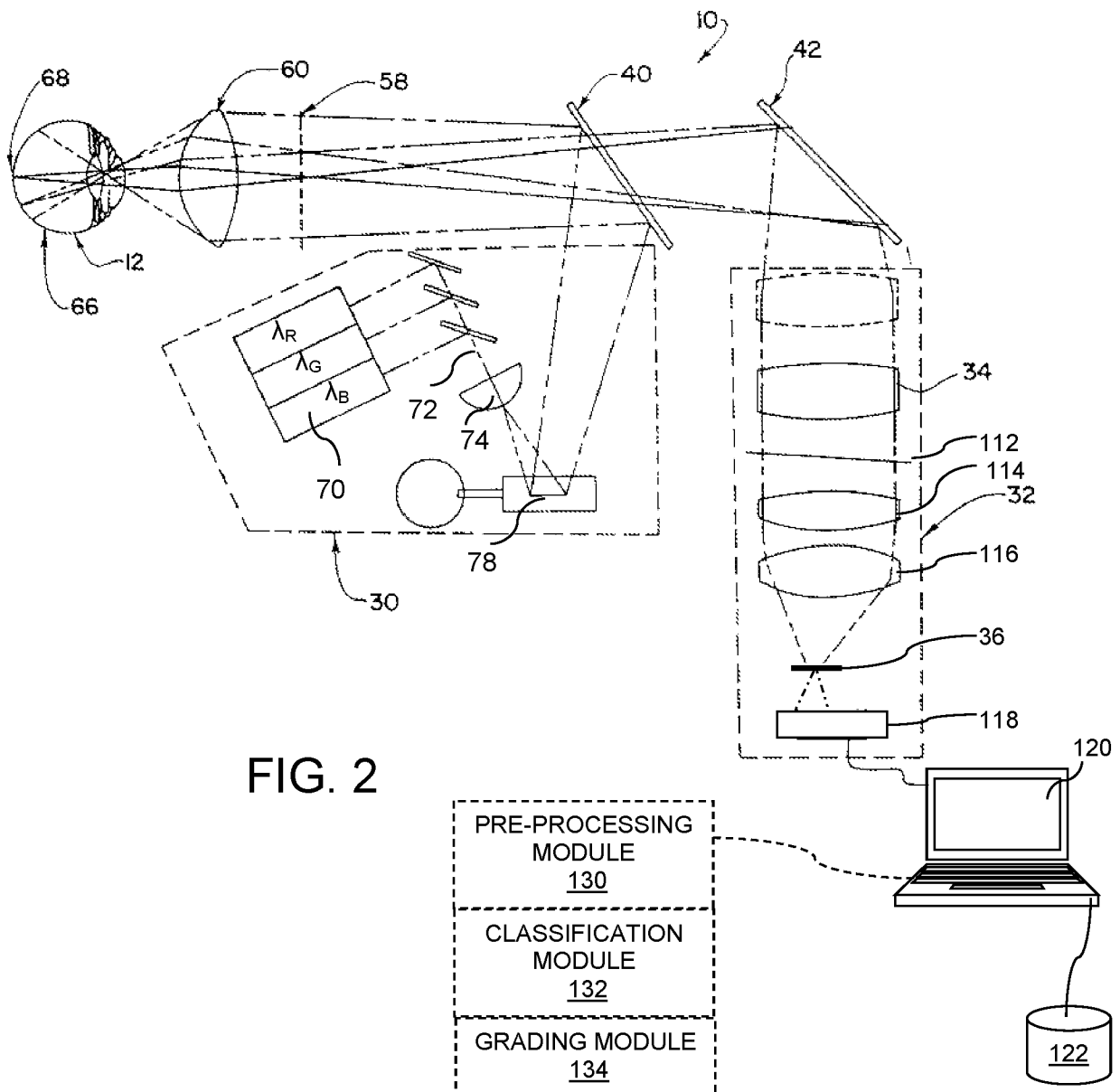


FIG. 1



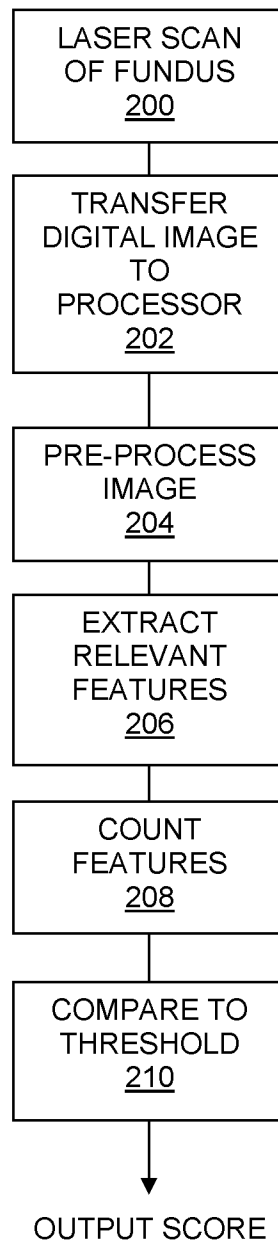


FIG. 3

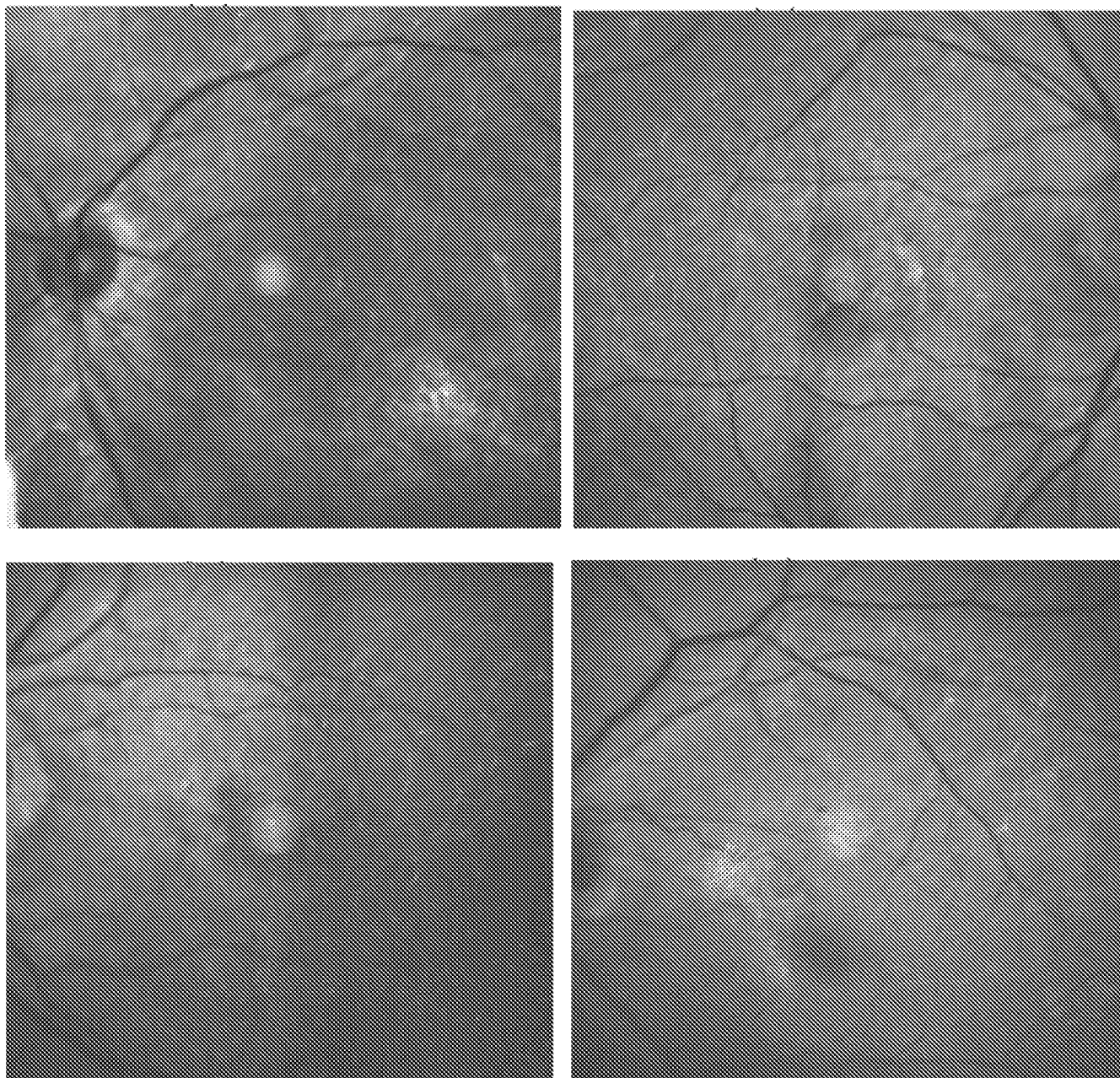


FIG. 4A

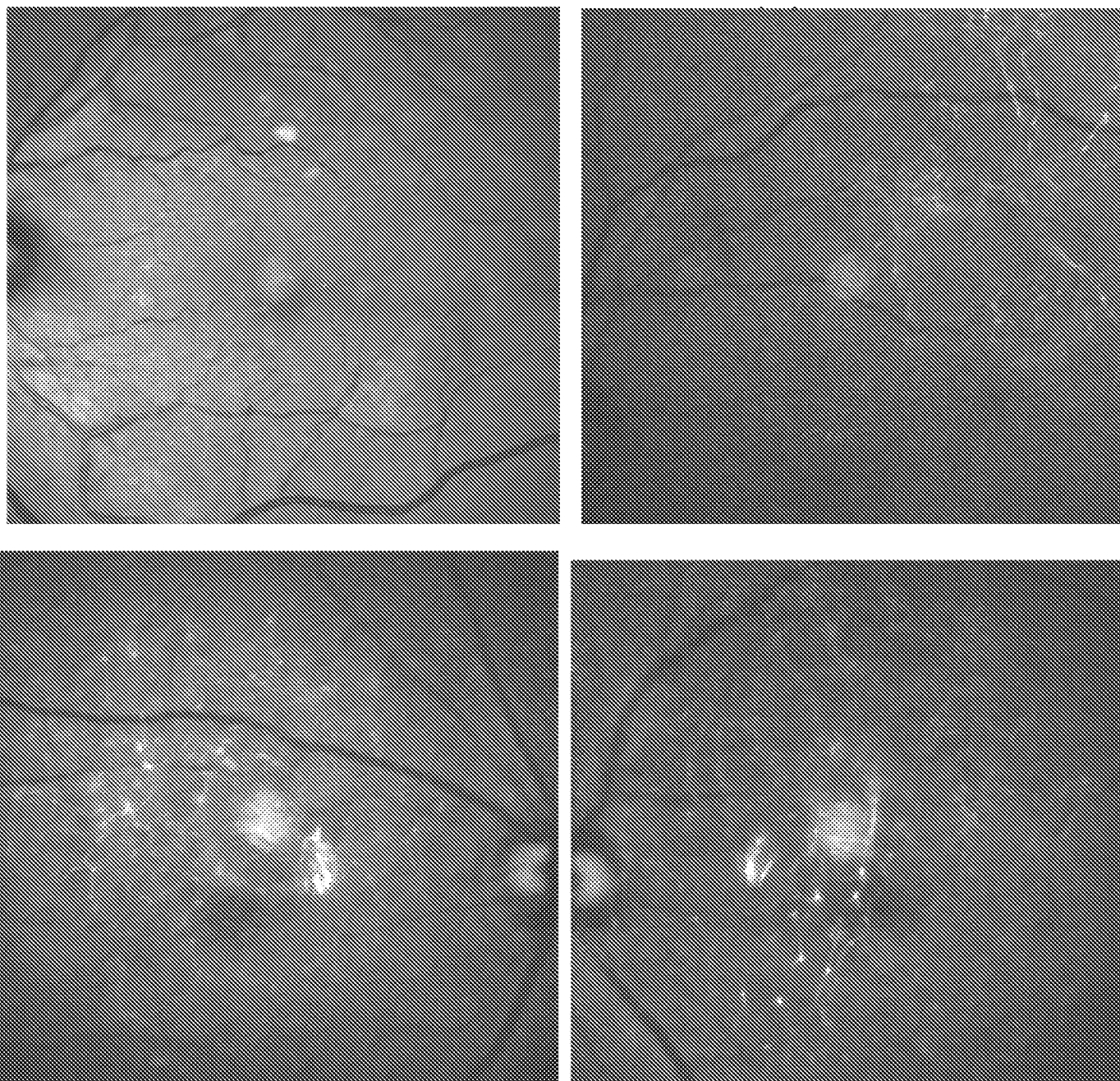


FIG. 4B

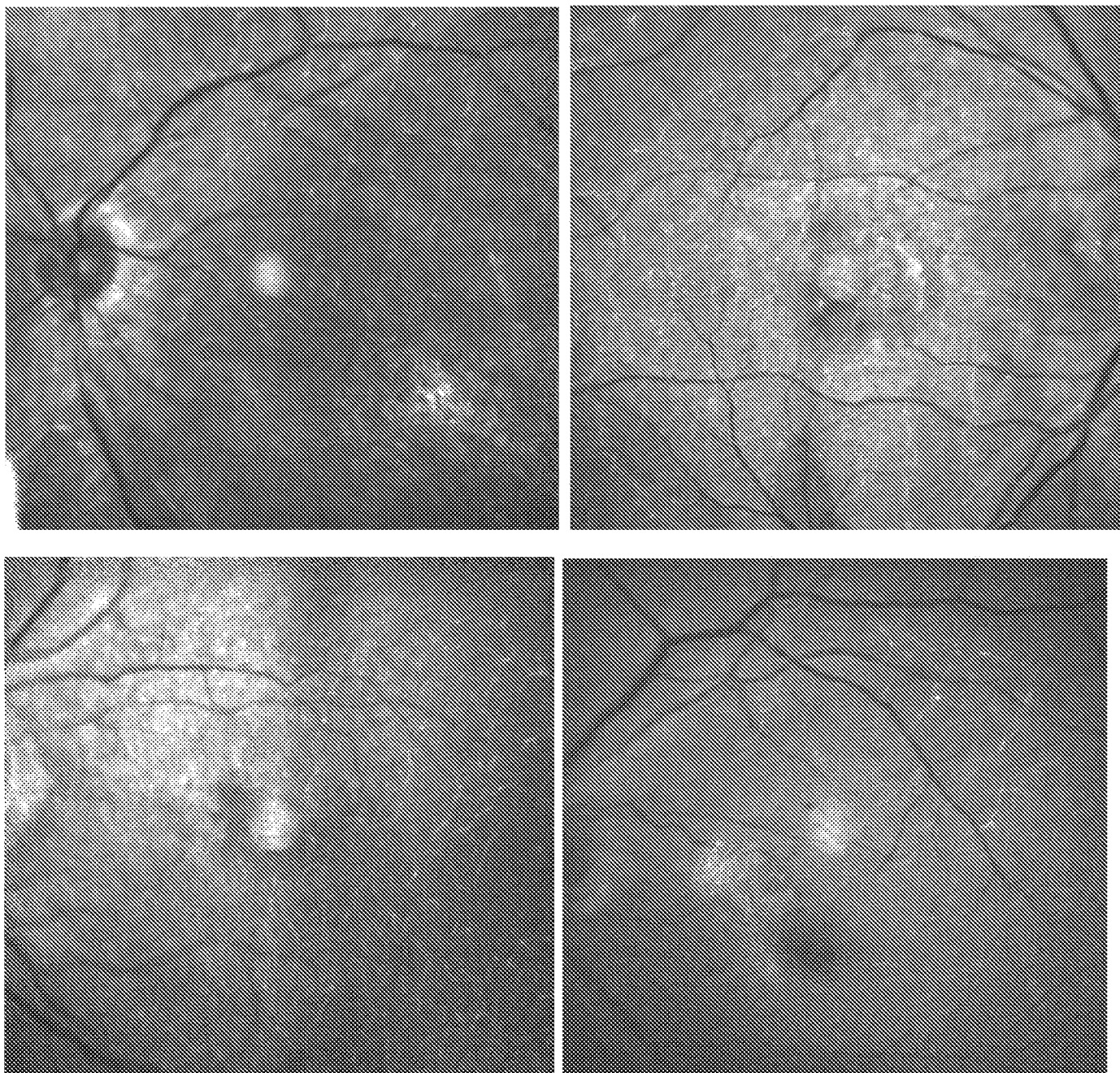


FIG. 5A

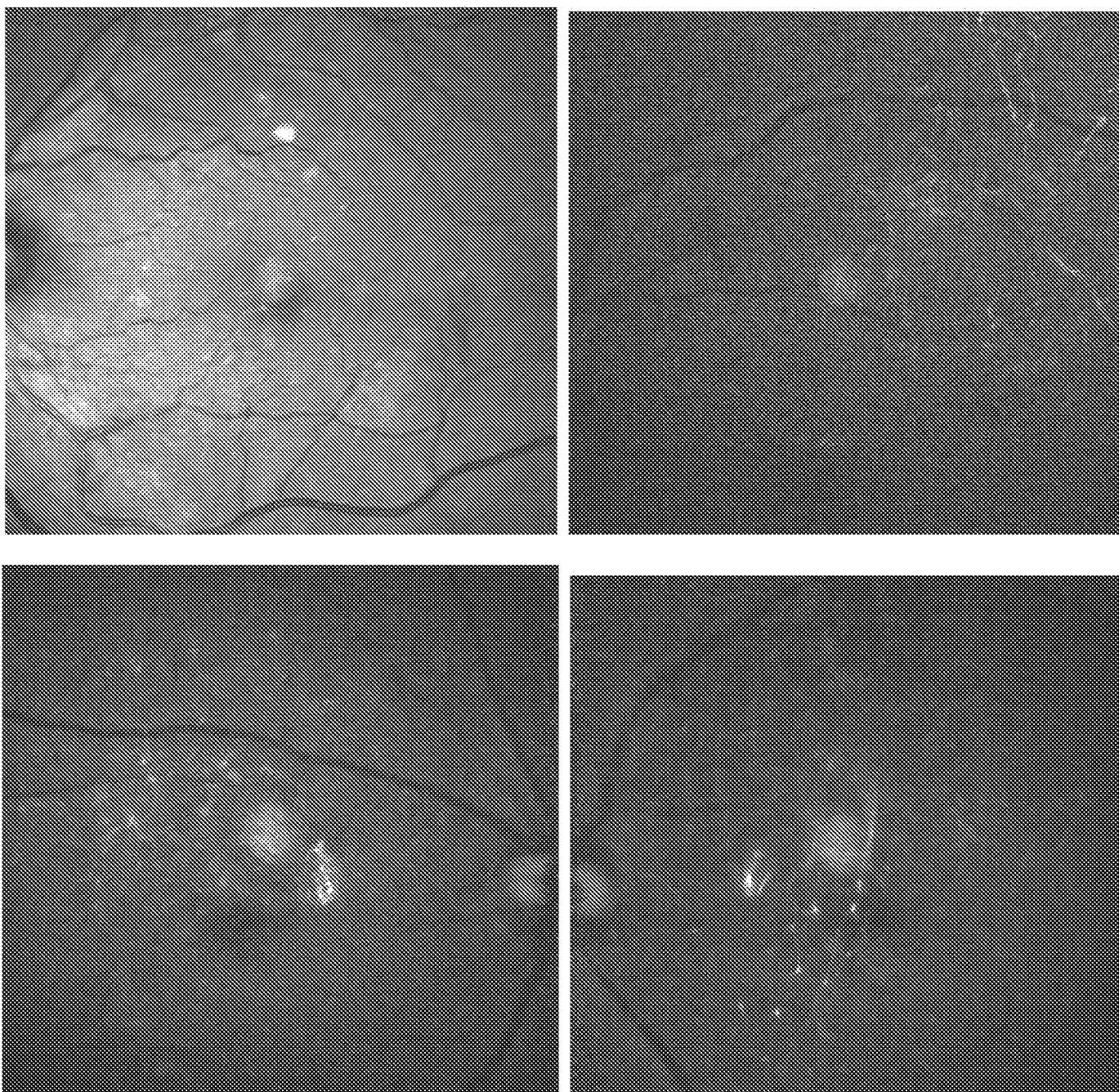


FIG. 5B

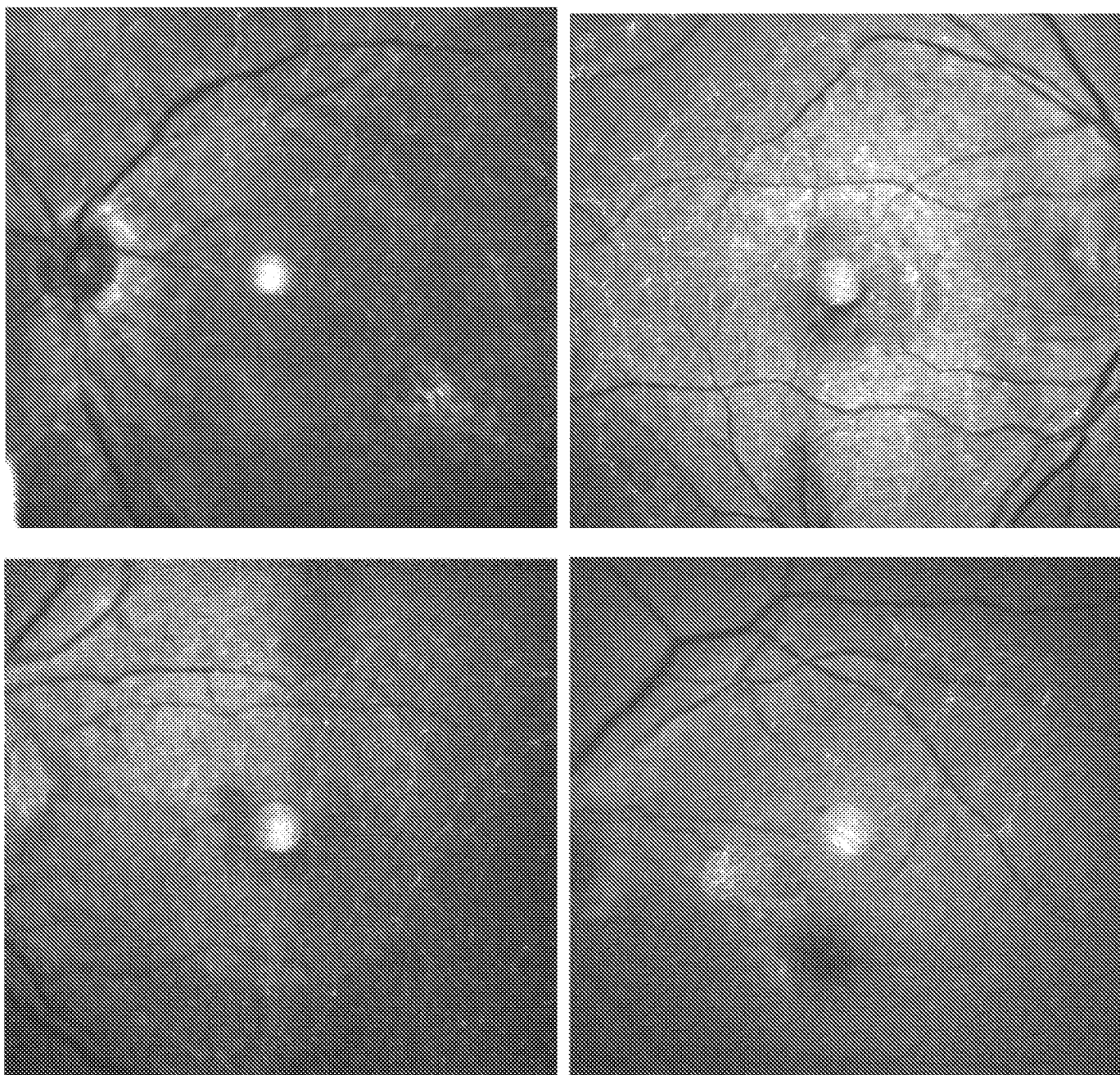


FIG. 6A

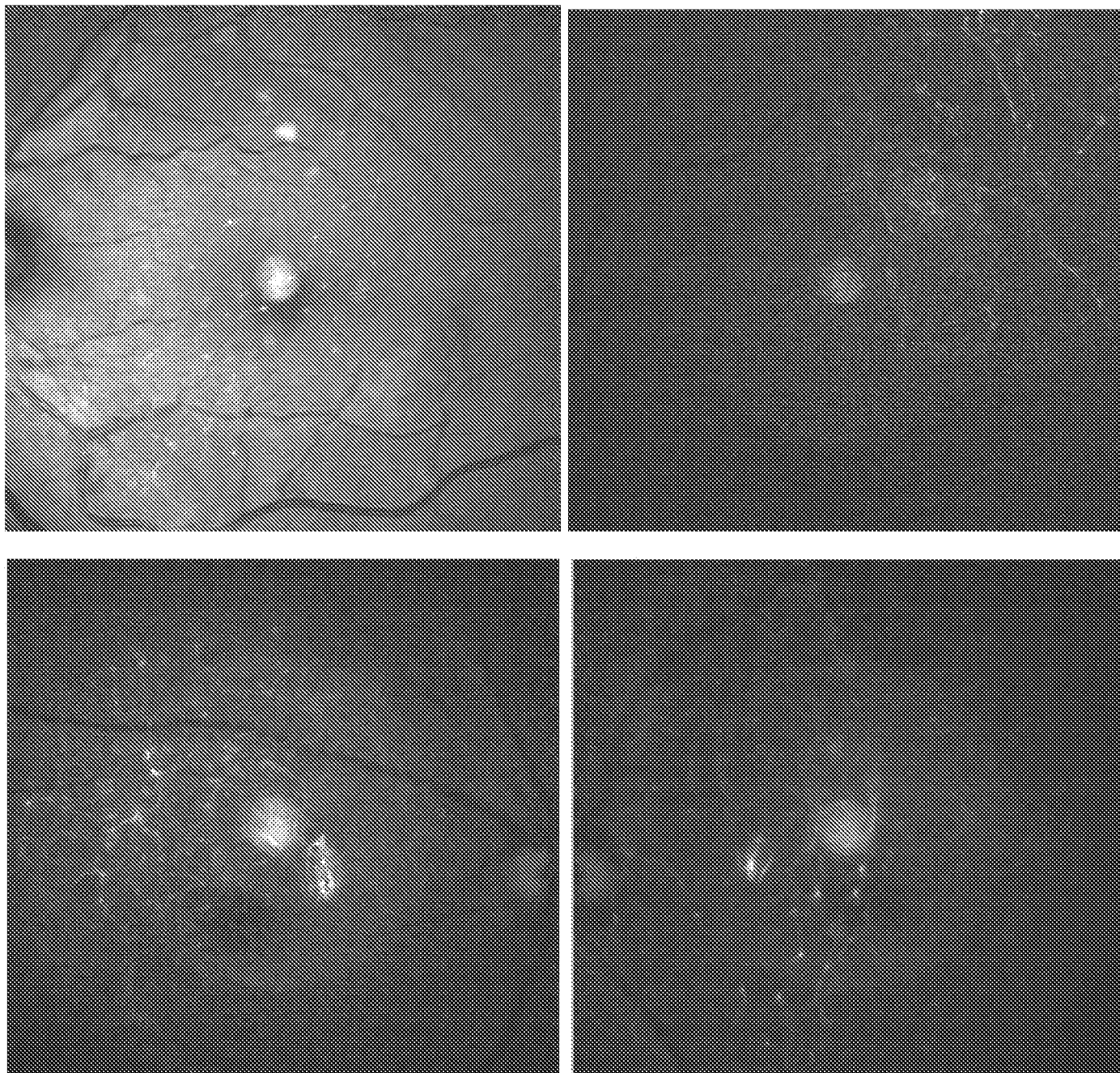


FIG. 6B

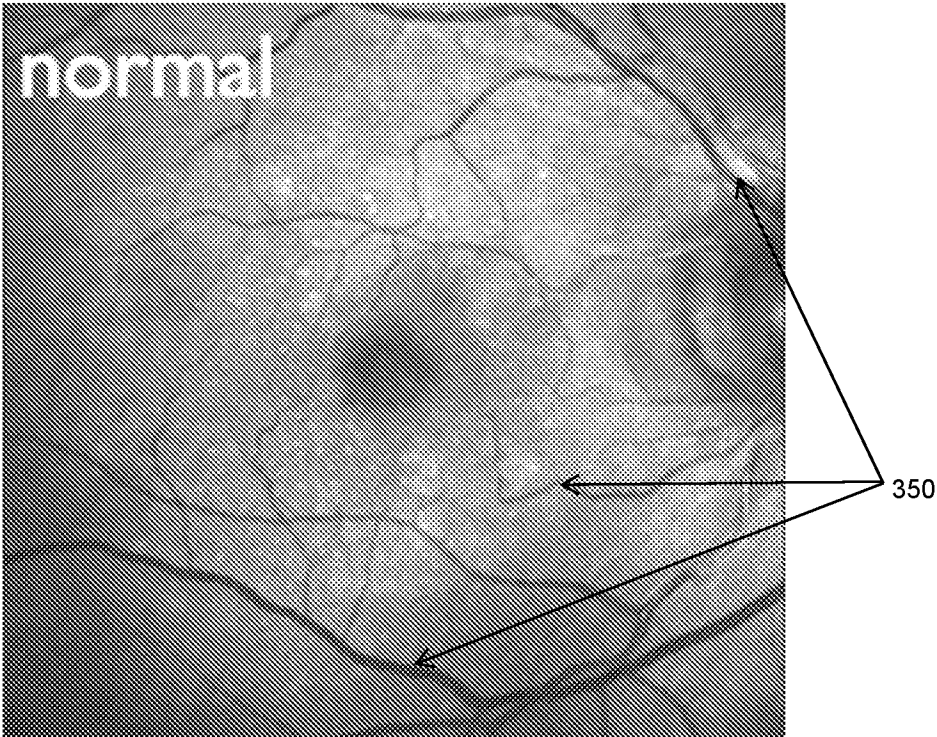


FIG. 7A

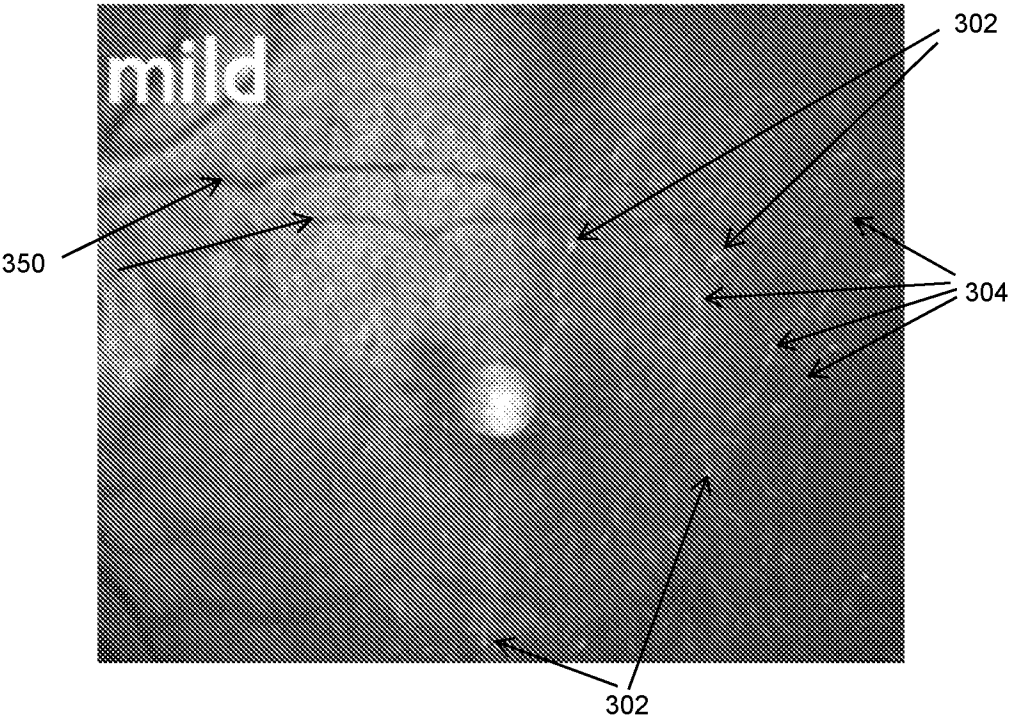


FIG. 7B

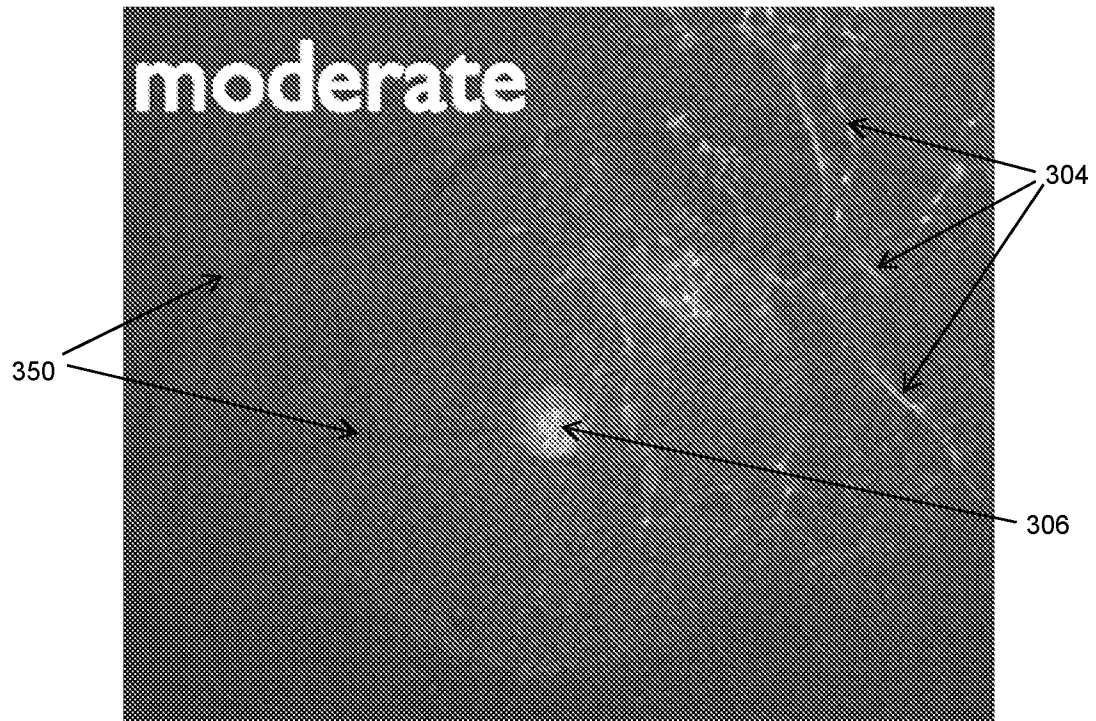


FIG. 7C

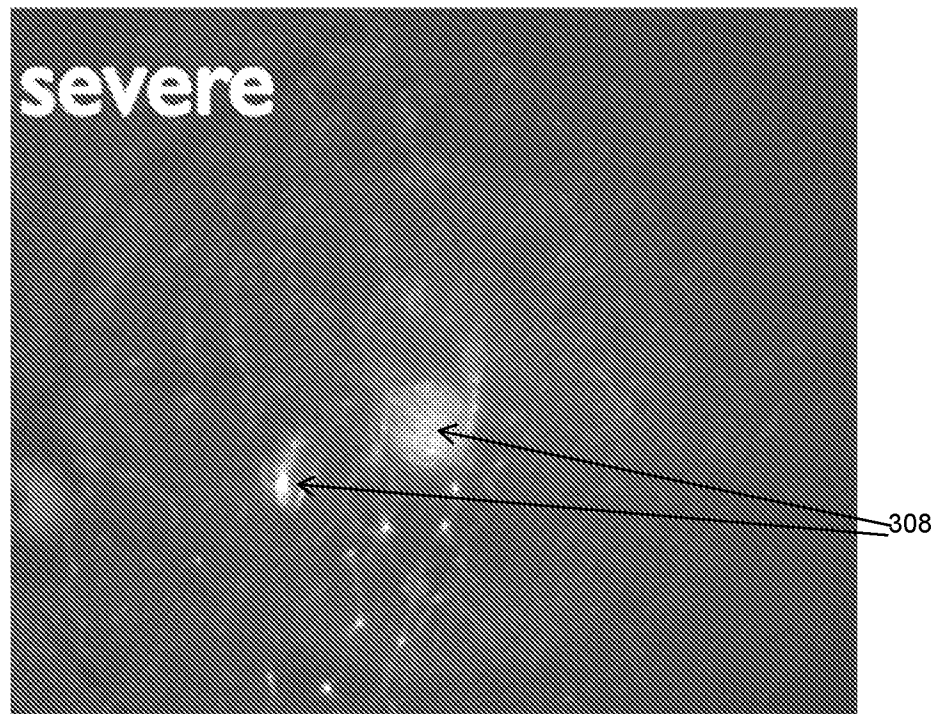


FIG. 7D

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/15811

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 3/14; A61B 3/13 (2016.01)

CPC - A61B3/00; G06T7/0012; G06T2207/30041

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61B 3/14; A61B 3/13 (2016.01)

CPC: A61B3/00; G06T7/0012; G06T2207/30041

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 351/246; 351/206 (Keyword limited, terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar (NPL); Keywords: dry eye, evaluate/monitor/diagnose, reticular pattern, cornea, image, scanning laser ophthalmoscope, backscatter, fundus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0109423 A1 (Wang) 25 May 2006 (25.05.2006) para [0010], [0011], [0012], [0030], [0036], [0039], [0040], [0042], [0046], [0047], [0049], [0066], [0069]	1-14
Y	US 2013/0295014 A1 (Boyd) 07 November 2013 (07.11.2013) para [0002], [0034], [0087], [0088], [0097], [0104], [0169], [0353]	1-14
A	US 2014/0300862 A1 (Perez et al.) 09 October 2014 (09.10.2014) para [0003], [0016], [0040], [0041], [0044], [0069]	1-14

☐ Further documents are listed in the continuation of Box C.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 March 2016 (15.03.2016)

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Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774