Incidence of Macular Degeneration in Older Women

Photograph Reading Manual of Procedures

Incidence of Macular Degeneration in Older Women: Photography Reading Center

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SOF

Photography Reading Center Manual of Procedures

The SOF Photographic Reading Center (PRC) is located in the Department of Ophthalmology in the School of Medicine at the University of California, Los Angeles. The staff consists of the following personnel: Director, Associate Director, Program Director, Computer Programmer, and Administrative Assistant.

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Personnel Responsibilities

Anne L. Coleman, M.D., Ph.D.: Director of the SOF Photography Reading Center (PRC), also serves as the Principal Investigator for Incidence of Late Macular Degeneration in Older Women. She is responsible for: (a) guiding the development of the PRC, (b) guiding the development of the computer programs used by the PRC, (c) monitoring the quality of the information produced by the PRC, (d) ensuring that PRC quality control procedures are being carried out properly, (e) helping provide direction for technician training and certification, (f) over-reading a random sample of photographs across the sites on a monthly basis for quality monitoring, (g) submitting reports on photography quality issues to SOF sites, (h) providing feed-back to the technicians based on the random sample overread of the photographs for quality control, (i) being available for questions regarding the clinical exam, and (j) adjudication of fundus findings of graders.

Carol M. Mangione, M.D., M.S.P.H.: Co-Principal Investigator. She is responsible for assisting with all aspects of the research, which include the following: (a) assisting with the development of the PRC, (b) ensuring that the photographs and data received by the PRC are handled in an appropriate manner, and (c) ensuring that data processing is carried out according to schedule.

Kent W. Small, M.D.: Retina Specialist. He will be responsible for (a) assisting with the development of the PRC, (b) ensuring that the photographs and data received by the PRC are handled in an appropriate manner, and (c) ensuring that data processing is carried out according to schedule and (d) adjudicating the fundus findings of the graders.

Colleen Gillis, CRA: Senior Photographer. She is responsible for the following: (a) communicating with the PI, the Co-PI, the Program Director and others involved in the collection, processing and archiving of data pertaining to this study as needed from the PRC, (b) communicating with the sites involved in the study to ensure that quality photographs are being produced by the technicians across the sites, (c) preparing film for processing as it is received, delivering film to processing company, picking up developed film, and helping to create the archive, (d) being available for questions from the sites, (e) training photographers at the sites, (f) reviewing and grading all fundus images for quality, (g) grading fundus images for AMD, and (h) grading lens.

Margarita Gonzalez: Project Coordinator. She is responsible for: (a) communicating with the sites involved in the study, (b) ensuring that the photographs and data are being processed appropriately and forwarded in a timely manner to the Data Coordinating Center (DCC or Fei Yu), (c) Providing direction to the sites for technician training and certification, (d) providing a random sample of photographs for the Director to over-read for quality control, (e) assisting in the development of a photography database for the study, (f) creating a monthly newsletter on the quality of the images and the data for the sites during data collection, and (g) organizing the quarterly meeting among the graders so that they can discuss difficult cases and adjudicate disagreement once they start to over read cases. She will be responsible for logging in the participants and placing each eye's

fundus photographs into a separate sleeve (2 sleeves/subject or 1/sleeve per eye per Visit). She will then create stacks of 20 eye's images for the graders to read the fundus photographs if it is Visit 8 and the fundus and lens photographs if it is Visit 6. She will be responsible for the maintenance of the photographic archive. She will work with Dr. Yu regarding the monthly cleaning of the data that is collected at the sites and will contact the sites when there are data entry errors or data cleaning issues that need to be addressed.

Richard Kratz, MD: Reading Center Grader. He is responsible for being back-up to the Senior Photographer. In addition, he is responsible for reviewing and grading some of the fundus images for quality, grading fundus images for AMD, grading lens images, and helping to create a newsletter on the quality of the photographs for the sites

Fei Yu, PhD, Cathy Zhou, BS Computer Programmers/ Statisticians: The computer programmers are responsible for creating a database file, providing reports on the quality of the photographs, and the data from the clinical sites. Dr. Yu and Ms. Zhou will also provide quarterly reports on the inter- and intra-grader reliability. They will create the random samples for the reliability assessment. They will provide the needed date and statistics for the newsletter. They will provide bi-weekly reports to the PI on the progress of the graders in grading the fundi and will help oversee the photographic archiving. They will generate the numbers for the Wisconsin Reading Center overreads. In addition, they will be responsible for the monthly cleaning of the clinical data that is collected at the sites. They will be responsible for the stratified sampling scheme of the subjects that participate in this study. In addition, they will be responsible for the all data management and analyses related to this study.

Other Resources for the Photography Center:

General Assistance with Fundus Photography Grading:

Margarita Gonzalez Address:	Telephone: (310) 794-4455 Jules Stein Eye Institute, UCLA 100 Stein Plaza, Room 2-118 Los Angeles, CA 90095 gonzalez@jsei.ucla.edu
Colleen Gillis Address:	Telephone: (407) 389-0800 Advanced Vision 2100 West State Road 434, Suite 1020 Longwood, FL 32779 cpgillis@hotmail.com
Richard Kratz, MD Address:	Telephone: 310-794-4455 Jules Stein Eye Institute, UCLA 100 Stein Plaza, Room 2-118 Los Angeles, CA 90095

kratz@jsei.ucla.edu

General Assistance with Canon Cameras:

Gary Rackler Technical Support Specialist Canon Medical Systems	Telephone: (972) 409-8872
Address:	Canon USA Email: grackler@cusa.canon.com

Film purchasing from Unique Photo:

Alan Bergson	Telephone: 800-631-0300
Address:	Unique Photo 11 Vreeland Road Florham Park, New Jersey 07932-0979

Film Processing from Photobition Orlando:

Tim Hoover	Telephone: 800-330-3578 407-660-0606
Address:	Photobition Orlando 505 Lake Destiny Drive Orlando, FL 32810

Slide storage pages from Adorama:

Sales	Telephone: 800-223-2500
Address:	Adorama 42 West 18th Street New York, NY 10011

Film Handling at the Clinical Sites Prior to Shipping to UCLA:

Film Processing:

Film will be sent to the Ms. Gillis via Federal Express weekly from the clinical sites. Even if the film does not have 6 subjects on it, it should be sent after 2 weeks for development. Partially exposed rolls of film may be removed after rewinding the film automatically by depressing the Manual Rewind Button (Appendix A, Page 30, Photo MOP). The photographer will attach a numbered film roll label to each exposed roll of film before sending it to Ms. Gillis. The film roll label appears as follows:

SOF- AMD

Date loaded:_____
Center #_____
Roll #:_____

The film roll number MUST correspond with the sequential number appearing on the corresponding Photography Film Log page. It is critical that a Xeroxed copy of the appropriate pages from the Photography Film Log accompany each roll of film.

Preparing the Rolls of Film for Processing by Colleen Gillis at Advanced Vision in Florida:

1. The undeveloped rolls of film arrive at Advanced Vision in Fed- Ex envelopes. The photographer will unpack and store these rolls as a group for the next processing batch. Batches are done twice a week.

2. Film logs are hole-punched if necessary. The log sheets are dated with the date received at the top of the page.

3. Ms. Gillis will confirm that each roll of film has the appropriate label that corresponds to the Photography Log Sheet included in the Fed-Ex package.

4. When all the canisters and corresponding Log Sheets are confirmed, the canisters are then placed in 2 Photobition processing bag. Along with the canisters is an instruction sheet with appropriate directions for mounting the fundus photos. In addition, **2 prepaid coupons for each canister of film** or the billing information is placed in the bag.

5. The bag is sealed tightly to help prevent loss of inserted materials. The package is then ready to be delivered to Photobition Orlando.

6. Ms. Gillis will have the film processed within two days so that the results can be reviewed as soon as possible for possible camera malfunctions. Also, the opportunity for photographers to critique their work is critical to the maintenance of satisfactory photographic quality.

Pick-up of Photographs:

1. Check for incoming processed film at Photobition Orlando. A previous batch of film is usually ready for pick-up when dropping off a batch to go out.

2. Unpack the boxes of slides carefully because the lid of the boxes might be loose.

3. Look for unexposed rolls or slide boxes that are not complete, which indicates camera/operator problems. If these are present, examine them and determine what caused the problem(s).

4. Talk to the Photographer at the clinical site as soon as possible and discuss the issue. Will notify the Project Coordinator and PI of any photographer or camera problems immediately.

5. Will do the quality grading on the images and enter the data into the Access database.

Sorting of Photographs

A light box and a viewer are necessary to examine and sort photographs. Recommended are the Logan Model 1055 slide sorter and a Larson Viewer designed for examining slides. The magnification of the loupe can range between 4X and 8X. Any lower magnification will not allow adequate visualization of retinal features; any higher magnification does not allow appreciation of the gestalt of the picture, and runs into the graininess of the film.

Labeling of Photographs

Each mount is identified on the bottom of the cardboard frame with a label on which is written or printed the name of the site, the patient identification number, and the eye (right or left). (AVERY laser labels #5267, ½" x 1-¾", 80 labels/sheet, 25 sheets/package) fit perfectly on the slide mounts. These labels are produced for each patient visit as soon as the photographs arrive at UCLA from Ms. Gillis in Florida. A copy of the log sheet will be provided to the Coordinating Center along with the slides for this purpose.

Labeling of Slides

All of the slide labels will be formatted as follows:

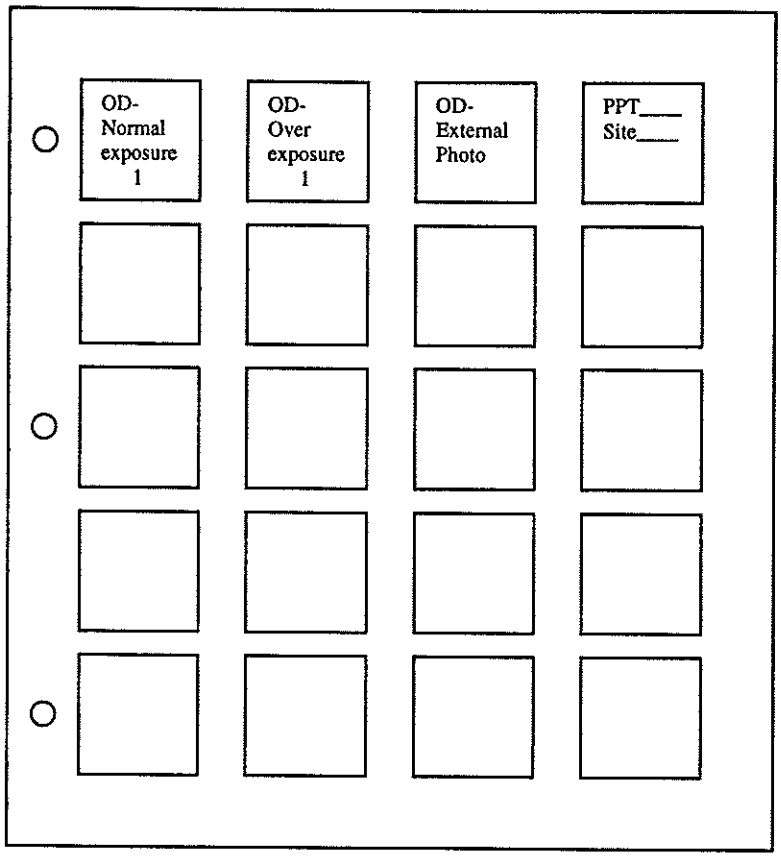
Each label will have the participant number and the eye (OD or OS) as shown below:

PPT: (ID Number) OD PPT: (ID Number) OS

Preparation of Photographs for Grading

The mounted and labeled transparencies are placed in 9" X 11" ***TRANSPARENT*** plastic sheets containing 20 pockets per sheet. The plastic sheets should be constructed so that the pockets ***open at the side*** rather than at the top; that is, the open side of the left pocket should face the open side of the right pocket. There is less chance of loss when the transparencies are mounted in this manner because they tend to press against each other and thus are held in place. **Please do not use frosted plastic pages.** Thin archival plastics are discouraged since they collapse on the inclined light tables used for grading. The Reading Center recommends slide pages from Adorama at 42 West 18th Street, New York City, NY, 10011, Telephone: 800-223-2500.

One plastic sheet (sleeve) should be used for each eye of each participant for each visit (1 sheet per eye per visit). The transparencies should be mounted so that the pocket openings face to the front, that is, face the person mounting the slides, and the edge with the three holes for a ring binder should be to the left of the mounted slides. The transparencies should be oriented for viewing in the arrangement diagrammed below.



Each page is labeled with a slide page identification label, as below, measuring 1 ¼ by 1 ¾ inch (Avery laser label #2028) containing the clinic name, patient identification number.

ID LABEL * UCLA

PPT:_____

SITE:_____

Fundus Photograph Grading Protocol

(BASED ON THE NHANES III FUNDUS PHOTOGRAPH GRADING PROTOCOL FOR 45 DEGREE PHOTOGRAPHS)

INTRODUCTION

Fundus photographs will be used to assess the presence of age-related maculopathy. The grading system used for age-related maculopathy is a modification of the grading and classification system used in the Beaver Dam Eye Study and the Framingham Eye Study that was developed by the University of Wisconsin Reading Center.

MATERIALS USED IN GRADING

Graders will use:

a) Larson viewer and a 10X Peak Lupe with a mm measuring grid installed;
b) Logan #1055 light board, modified to hold two 14 watt "daylight" fluorescent tubes;
c) Field definition grid;
d) Two standard grids: Grid A for delineating 3 areas on the 45 degree fundus photos: area outside the arcade, the arcade area (8250 microns diameter- 5500 microns diameter in 30° photos) and central circle area (2250 microns diameter- 1500 microns diameter in 30° photos)*. Grid B for defining macula area for quality gradings (4500 microns diameter in 45° photos– 3000 microns diameter in 30° photos)*.
e) Standard circles for grading drusen area: C_0=95 microns diameter (63 microns diameter in 30° photos), C_2=375 microns diameter (250 microns diameter in 30° photos), O_2=960 microns diameter (640 microns diameter in 30° photos)*;
f) Two non-stereo 45-degree fundus photographs, mounted in plastic sheets, taken with a Canon non-mydriatic fundus camera;

(*The standard grid measurements are calculated based on measurements using grids developed for use in grading using a 30° degree camera)

GRADING PROCEDURES

Four 45° fundus photographs are available for each participant, two for each eye, along with two red reflex, external photographs, one for each eye. Since more than 1500 Visit 6 images have been read, Visit 8 fundus photographs will be graded using the same grading system developed for Visit 6. Graders will not grade both eyes of an individual at the same time. In addition, all fundus images will be read by at least 2 graders.

Discrepancies between graders will be adjudicated with Drs. Coleman or Small. All graders will be masked to the findings in the other eye and at the other visit.

QUALITY GRADING

FUNDUS:

If a fundus photograph is present, the grade is 'Present', code "2"; if the fundus photograph is not present, the grade is 'Absent', code "0", STOP. When a photo is present, but the fundus is entirely obscured the fundus is graded as 'Absent', code "0". For instance, if there is no fundus detail visible and it is impossible to judge whether the fundus photograph is of a right or left eye, the photograph is considered absent. However, if any fundus detail is discernable and/or there is even a suggestion of a lesion, the grade is 'Present', code "2", and the proceeding items should be answered until another stop condition is met.

FOCUS:

Focus refers to the clarity of retinal image. Because of the importance of detecting lesions in the macular area, the grader is to consider focus in 75% or more of the macula area as defined by the 4500 microns diameter circle of grid B.

If retinal vessels are sharply defined or slightly fuzzy and small lesions, such as retinal microaneurysms and small drusen are visible, the grade is 'Good/Fair', or code "0". If clarity is decreased so that small retinal lesions might be missed but larger lesions, such as geographic atrophy, can be seen, the grade is 'Borderline', or code "1". If there is a pronounced decrease in sharpness, where detail of larger lesions cannot be recognized, the grade is 'Poor', or code "2".

FIELD DEFINITION:

The photograph is positioned on the field definition grid. A fundus photograph with the optic disc positioned entirely within the dotted line of the grid is considered 'Good', code "0". The grader proceeds to whether artifacts are present. A fundus photograph with any portion of the optic disc positioned between the dotted line and the solid line is considered 'Fair', code "1". A fundus photograph with any portion of the optic nerve positioned outside the solid line on the grid is considered 'Poor', code "2". A photograph with either 'Fair' or 'Poor' field definition is further defined in terms of Horizontal/Vertical Field Definition.

FIELD DEFINITION HORIZONTAL:

If the entire optic disc is within the dotted line of the grid, so that all of the optic disc, the macula and temporal retina are visible, the grade is 'Good', code "0". If any portion of the temporal edge of the optic disc is outside the dotted line of the grid, the grade is 'Temporal', code "1". If any portion of the nasal edge of the optic disc is outside the

dotted line of the grid, the grade is 'Nasal', code "2". If horizontal field definition cannot be determined, the grade is 'CG', code "8".

FIELD DEFINITION VERTICAL:

If the optic disc is entirely located within the dotted line of the grid, the grade is 'Good`, code "0". If any portion of the superior edge of the optic disc is outside the dotted line of the grid (that is, the vertical orientation is "high") the grade is `High', code "1". If any portion of the inferior edge of the optic disc is outside the dotted line of the grid, (that is, the vertical orientation is "low") the grade is 'Low', code "2". If the vertical field definition cannot be assessed, the grade is 'CG', code "8".

ARTIFACT PRESENT:

If there is no artifact present, the grade is 'No', code "0". Proceed to whether the fundus is gradable or not (gradeability). If there is an artifact present, the grade is 'Yes', code "2", and the specific artifact(s) is/are checked in the appropriate item as:

Haze A green/white halo or partial halo, or a green/white cast throughout the photograph, see NHANES artifact examples;

Dust see NHANES artifact examples;

Lashes see NHANES artifact examples;

Arc A sharp edged band on the edge of the field ranging in color from white to orange, often blue tinged, usually extending no more than 180 degrees. See NHANES artifact examples;

Uneven Illumination, Center see NHANES artifact examples;

Uneven Illumination Edge see NHANES Standard #7B;

Central Dot Artifact see NHANES Standard #8;

Other if 'Other' is noted, describe the artifact in Comment section.

GRADEABILITY:

If the whole field can be graded, the grade is code "0". If the disc cannot be graded, but it is possible to grade the macula, the grade is code "1", 'Disc ungradeable'. If a portion of the macula $\geq O_2$ and less than 75% of macula (4500 diameter microns, Grid B) cannot be graded, but the disc is gradable, the grade is code "2", 'Portion macula ungradeable'. If $\geq$ 75% of the macula area (4500 diameter microns, Grid B) is in 'Poor' focus, or is missing, or is obscured by a retinal hemorrhage, vitreous hemorrhage, asteroid hyalosis or some other condition and no lesion of any type is seen, but it is possible to grade the disc, the

grade is code "3", 'Macula ungradeable'. However, if any lesion is questionably present or present in the remaining 25% of the macula, the photo is graded and the appropriate gradeability is chosen (either code "2" or code "4"). If a portion of the disc and the macula are ungradeable, the grade is code "4". If neither the disc nor the macula can be graded, but other portions of the eye are visible, the grade is code "5". If none of the field can be graded, the grade is code "6". If code "6" is chosen, STOP.

READING CENTER-PHOTOGRAPHER COMMUNICATION

As film is received by Ms. Gillis, it will be developed and the photographs will be graded for quality. Weekly, the Senior Photographer will review the quality of each photographer's work with the Program Director and PI at UCLA. The Senior Photographer or Program Director will then call the site photographers by telephone to discuss any significant problems observed. This contact will also allow the site photographers an opportunity to ask questions or make comments.

When substantial problems are observed (particularly if a photographer has reverted from full to provisional certification), the Senior Photographer will phone the photographer more frequently and update the Program Director on the progress being made to improve the photographer's quality. If the problems cannot be adequately addressed by telephone, the Senior Photographer may arrange to conduct a special photographic site visit for the purpose of observing the photographer at work and demonstrating the desired technique.

Monthly, the UCLA Coordinating Center will issue a newsletter for study technicians, regarding issues of particular interest to them and discussing methods for obtaining the most optimum results in data collection. Comparisons of dilation rates and quality of fundus images will be made.

FUNDUS GRADING

GENERAL PRINCIPLES WITH GRADING

1 A lesion is definitely present if the grader is 90% or more sure.
2 A lesion is questionably present if the grader is 50% to 89% sure.
3 A lesion is absent if the grader is less than 50% sure.
4 Grids A and B are placed behind the slide.
5 With Standard 2A, the grader is interested in the area of hemorrhage not the density. The area of hemorrhage in Standard 2 A is equivalent to 9 O_1's.
6 On the 45 degree photographs venous beading can only be graded on the major veins.
7 On the 45-degree photographs anything that is suggestive of edema in the macular area is Clinically Significant Macular Edema (CSME).
8 Microaneurysms are less than 125 microns (the approximate width of the vein at the disc margin). It is a hemorrhage if it is larger than 125 microns.

AGE-RELATED MACULAR DEGENERATION

Any Drusen Present

In order to assess further information about drusen, the grader must first answer the gatekeeper question code "2". If the eye can be graded and there are no drusen present within the field the grade is 'No', code "0". The grader then proceeds to the Comment Section.

If a drusen is present or questionably present anywhere in the field or there are some, but not all, items which should be listed as CG, code "8", the grade is 'Yes', code "2".

If it is impossible to assess whether a hard or soft drusen is present in 75% of the macula, using Grid B, 4500 μ diameter, and no drusen are present in the remaining 25% of the area, the grade is 'Can't Grade', code "8". In the situation where it is impossible to grade for hard drusen, but the grader is able to assess the presence or absence of soft drusen, a grade of 'Yes', code "2", is chosen. The grader should answer the hard drusen question "8" and consider the area questions as only referring to soft drusen.

Hard Drusen Present

Hard drusen are less than 95 μ in size by definition and thus the edges of hard drusen do not go outside the Standard circle C_0. A drusen that is larger than C_0 is a soft drusen. If there are no hard, punctate retinal drusen present, the grade is code "0" and the grader goes on to Soft Drusen. If the grader is from 50% to 90% certain that there are hard drusen present, that is, drusen that are more subtle or that are questionably present, the grader treats it as Indistinct Hard Drusen (The grade is "Questionable", code "1" in Visit 6). If there are definite hard drusen present anywhere in the field (90% or more certain), the grade is Distinct Hard Drusen - 'Yes', code "2". If $\geq$ 75% of the photograph cannot be graded, and no hard drusen are seen, the grade is 'CG', code "8".

Soft Drusen Present

If no soft drusen are present, that is, large drusen with distinct or indistinct margins (size is equal to or greater than Standard circle C_0), the grade is 'None', code "0". If the grader is from 50% to 90% certain there are soft drusen present anywhere in the photograph, the grader grades it as Questionable. If the grader sees soft drusen with hard edges anywhere in the photograph, the grade is Distinct Soft Drusen - 'Yes', code "2". If the grader sees soft drusen with indistinct, blurry edges anywhere in the photograph, the grade is Indistinct Soft Drusen – Yes, code "2". If $\geq$ 75% of the photograph cannot be graded, and no soft drusen are seen, the grade is 'CG', code "8".

Central Circle-Soft Drusen Present

If there are no soft drusen present within the central circle area of the grid, the grade is 'None', code "0". If soft drusen are questionably present in this area of the grid, that is, the grader thinks the likelihood of presence of soft drusen is between 50-90%, the grade

is 'Q', code "1". If soft drusen are definitely present in the central circle area the grade is 'Yes', code "2". If 75% or more of the central circle area using Grid A cannot be graded, and the grader does not see soft drusen in the remaining 25%, the grade is 'CG', code "8".

Inner Circle-Soft Drusen Present

If there are no soft drusen present within the inner circle area of the grid, the grade is 'None', code "0". If soft drusen are questionably present in this area of the grid, that is, the grader thinks the likelihood of presence of soft drusen is between 50-90%, the grade is 'Q', code "1". If soft drusen are definitely present in the inner circle area the grade is 'Yes', code "2". If 75% or more of the inner circle area using Grid A cannot be graded, and the grader does not see soft drusen in the remaining 25%, the grade is 'CG', code "8".

Central Circle Area

If no drusen are present within the central circle area of Grid A, mark 'None', code "0". If the total area of drusen within the central circle of the grid is: $<C_0$, the grade is code "1"; $<C_2$, the grade is code "2"; $<O_2$, the grade is code "3"; $\geq O_2$, the grade is code "4". If 75% or more of the central circle area of Grid A cannot be graded, and nothing is present in the remaining 25%, the grade is 'Can't Grade', code "8".

Inner Circle Area

If no drusen are present within the inner area, that is, between the central circle boundary and the outer edge of the grid, the grader chooses 'None', code "0". If the total area of drusen within the inner area of the grid is: $<C_0$, the grade is code "1"; $<C_2$, the grade is code "2"; $<O_2$, the grade is code "3"; $\geq O_2$, the grade is code "4". If 75% or more of the inner area of Grid A cannot be graded, and no drusen are present in the remaining 25%, the grade is 'CG', code "8".

Area Outside the Grid

The grader again looks at Grid A centered on the fovea. If there are no drusen present outside this grid, the grade is 'None', code "0". If definite 'hard and/or 'soft' drusen are present outside the grid, the grader again compares the total area outside the grid with the set of Standard Open Circles. 'Questionable' drusen are not included in estimates of area. If the total area of definite drusen outside the grid is < Std. C_0, the grade is code "1". If the total drusen area outside the grid is < Std. C_2, the grade is code "2". If the total drusen area outside the grid is < Std. O_2, the grade is code "3". If the total drusen area outside the grid is $\geq$ Std. O_2, the grade is code "4". If the drusen area outside the grid cannot be assessed, the grade is 'CG', code "8".

Increased Pigmentation

Deposition of granules or clumps of grey or black pigment in or beneath the retina. (NHANES Abnormalities Example #6).

RPE Depigmentation

Degeneration or depigmentation of retinal pigment epithelium characterized by faint greyish-yellow or pinkish-yellow areas of varying density and configuration without sharply defined borders. Increased or hyperpigmentation is frequently seen over and adjacent to these areas. (NHANES Abnormalities Example #1).

Geographic Atrophy

Sharply defined area of drop-out of retinal pigment epithelium and choriocapillaries, exposing choroidal vessels. (NHANES Abnormalities Example #2).

Sub-retinal Hemorrhage

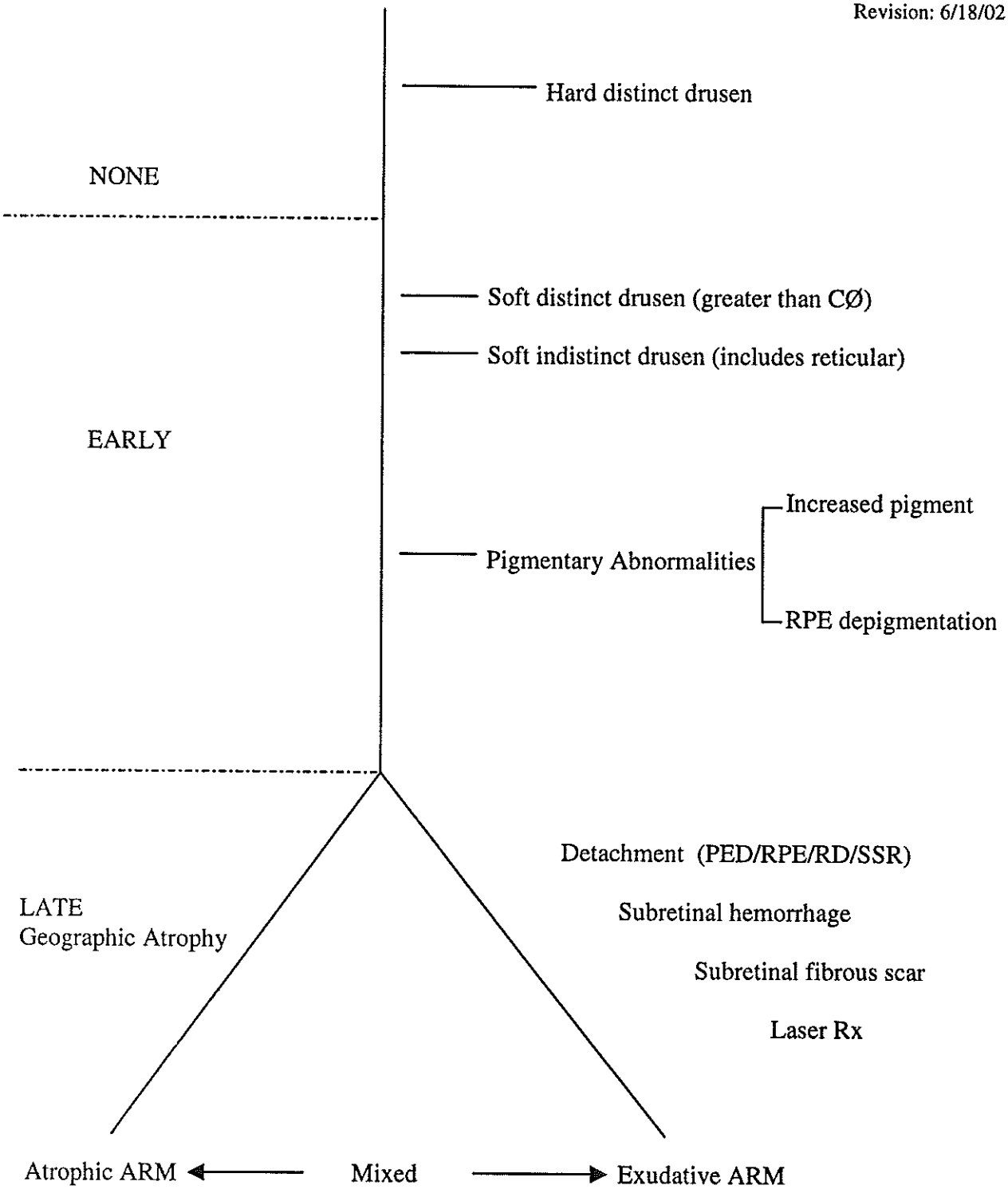
Hemorrhage below the retinal surface, which may appear as a dark red, dark grey or greenish area. (NHANES Abnormalities Example #3).

Sub-retinal Fibrous Scar

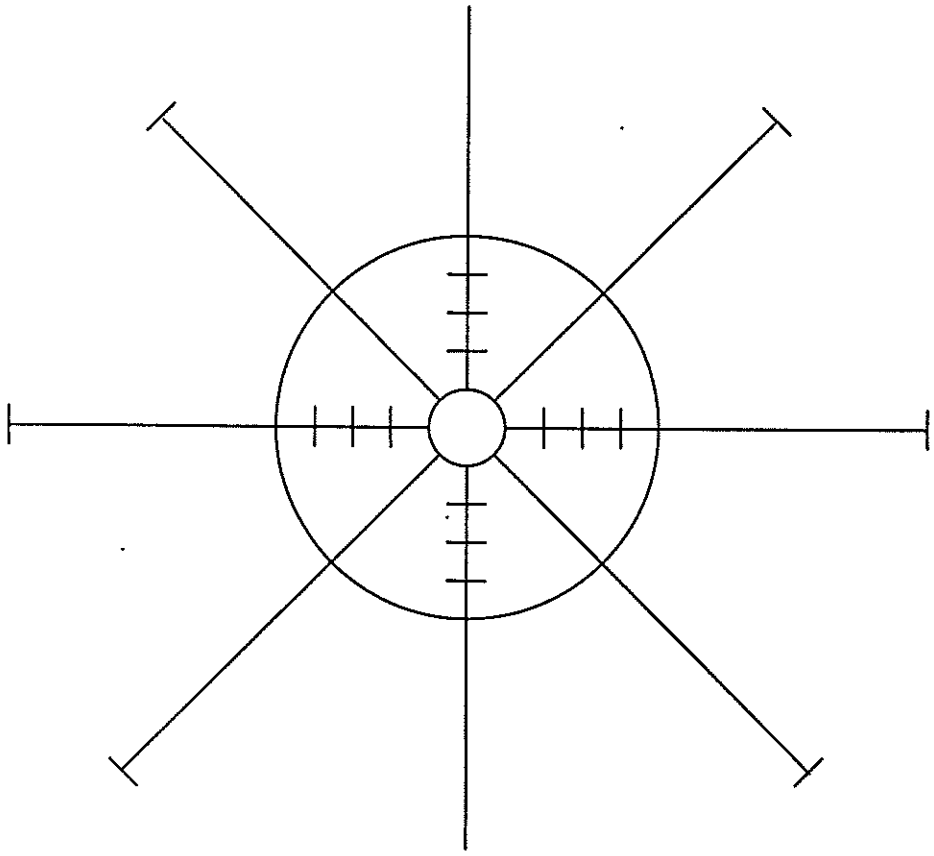
Sheets or mounds of "white" material appearing like a scar, involving the retina. (NHANES Abnormalities Example #4).

SSR Detachment

Clear or solid, dome shaped fluid filled elevation indicating a serous or retinal pigment epithelium detachment of the retina. (NHANES Abnormalities Example #5).


Hard distinct drusen
NONE
Soft distinct drusen (greater than CØ)
Soft indistinct drusen (includes reticular)
EARLY
Increased pigment
Pigmentary Abnormalities
RPE depigmentation
Detachment (PED/RPE/RD/SSR)
Subretinal hemorrhage
Subretinal fibrous scar
Laser Rx
LATE
Geographic Atrophy
Atrophic ARM
Mixed
Exudative ARM

Grid A:



50124

Eye Photo

Office Use Only
SOF ID# | Acrostic | Staff ID#

IF INTRAOCLULAR PRESSURE WAS NOT CHECKED, DO NOT DILATE. TAKE THE PHOTOS WITHOUT DILATING THE EYES.

IF THE ANSWER TO QUESTION 7, 8, OR 9 ON THE INTRAOCULAR PRESSURE FORM WAS ANSWERED YES, DO NOT DILATE. TAKE EYE PHOTOS WITHOUT DILATING THE EYES. OTHERWISE, DILATE AND THEN TAKE EYE PHOTOS.

(1) **Record the diameter of the pupils in mm PRIOR to dilating to help determine if the participant is dilated. It the participant did not have one or both eyes dilated due to criteria above, record diameter after 10 minutes in a dark room or after patched for 10 minutes.**

RIGHT EYE Before dilation: ☐☐.☐ **mm** **After dilation:** ☐☐.☐ **mm**

○ dilating drops not used

LEFT EYE Before dilation: ☐☐.☐ **mm** **After dilation:** ☐☐.☐ **mm**

○ dilating drops not used

(2) **Were photos of RIGHT EYE taken?** ○ Yes ○ No

(3) **Were photos of LEFT EYE taken?** ○ Yes ○ No

Canon Fundus Photos **Film Roll #** ☐☐☐ **Film Type** ☐☐☐

Check as completed:

	RIGHT EYE	LEFT EYE
a. (N) Photo #1	○ Yes ○ No	○ Yes ○ No
b. (+) Photo #2	○ Yes ○ No	○ Yes ○ No
c. External #3	○ Yes ○ No	○ Yes ○ No
d. Retakes?	○ Yes ○ No	○ Yes ○ No

Comments on photos:_____

Incidence of Late Macular Degeneration in Older Women
PHOTO QUALITY GRADING KEY

Reader ID (Initials)	Site (#)	Examiner	Photo Date	Subject ID	Date Processed	Subject Dilated OD OS OU Yes No
_____	___	_____	__/__/__	_____	__/__/__	

CANON PHOTOS

Patient ID# entered? No=0 Yes=2 ******** Date Entered? No=0 Yes=2

FUNDUS

Fundus: Absent=0 Present=2

Focus: Good/Fair=0
Borderline=1 (CG small drusen or MA)
Poor= 2

Field Definition:
Good=0
Fair=1
Poor=2
CG=8

Horizontal:
Good=0
Temporal=1
Nasal=2
CG=8

Vertical:
Good=0
High=1
Low=2
CG=8

ARTIFACTS

	NO=0	YES=2
Haze:	0	2
Dust:	0	2
Lashes:	0	2
Arc:	0	2
Blink:	0	2
Drooping Eyelids:	0	2
Center Illumination:	0	2
Edge Illumination:	0	2
Central Dot Artifact:	0	2
Other Artifact:	0	2

GRADABILITY: Circle one answer below

Entire field gradable	0	Disc ungradeable	1
Portion macula ungradeable	2	Macula ungradeable	3
Portion disc/macula ungradeable	4	Disc and Macula ungradeable	5
Entire field ungradeable	6		

SOF-AMD Photo Grading Form

Study ID: _____ Eye (R/L): _____ (1=Right, 2=Left)

Grader ID: _____ Date graded: _____

(1=CG, 2=RK, 3=ALC, 4=KWS, 5=JRA)

Photograph PRESENT (1/0): _____ If photograph PRESENT, enter "1". Otherwise, enter "0".

FUNDUS

Optic Nerve

Vertical Cup / Disc: _____ / _____

Horizonal Cup / Disc: _____ / _____

Thinning/Notching of rim: _____ (0=No, 1=Quest, 2=Yes, 8=CG)

Disc hemorrhage _____

Peripapillary Atropy/

Scleral crescent _____

Tilted _____

Abnormal Disc _____

Comment for optic disc: _____

Macula Grading (Grid A only)

Any drusen present? _____ (0=No, 1=Quest, 2=Yes, 8=CG)

Hard distinct drusen? _____

Hard indistinct drusen? _____

Soft distinct drusen? _____

Soft indistinct drusen? _____

Center circle soft drusen? _____

Inner circle soft drusen? _____

Outside grid area soft drusen? _____

Calcified drusen? _____

Reticular drusen? _____

Soft Distinct Drusen Area (0=None, 1= $<C_0$, 2= $<C_2$, 3= $<O_2$, 4= $>O_2$, 8=CG)

Center circle area _____ (C_0 = 63μ/95μ, C_2 = 250μ/375μ, O_2 = 640μ/960μ)

Inner circle area _____

Outside grid area _____

Soft Indistinct Drusen Area (0=None, 1= $<C_0$, 2= $<C_2$, 3= $<O_2$, 4= $>O_2$, 8=CG)

Center circle area _____ (C_0 = 63μ/95μ, C_2 = 250μ/375μ, O_2 = 640μ/960μ)

Inner circle area _____

Outside grid area _____

Drusen Area (Combined soft and hard drusen) (0=None, 1= <C_0, 2= <C_2, 3= <O_2, 4= >O_2, 8=CG)

Center circle area _____ (C_0 = 63μ/95μ, C_2 = 250μ/375μ, O_2 = 640μ/960μ)

Inner circle area _____

Outside grid area _____

Maculopathy (0=No, 1=Quest, 2=Yes, 8=CG)

Increased pigment _____

RPE depigmentation _____

Geographic atrophy _____

Sub-retinal hemorrhage _____

Sub-retinal fibrous scar _____

SSR detachment _____

PED detachment _____

	FIELD (0=No, 1=Quest, 2=Yes)	CENTER CIRCLE (0=No, 2=Yes)
Rx for ARM	_____	_____

Comments for Macula grading: _____

Diabetic Retinopathy Grading

Diabetic Retinopathy Level _____

10=No Retinopathy	11=Quest retinopathy
12=Non-diab retinopathy	14=HE, SE, IRMA w/o MA's
31=Early non-prolif	41=Mod non-prolif
51=Severe non-prolif	60=FP only
65=PDR < HRC	70=PDR ≥ HRC
80=Total VH	88=CG

HMA _____ 0=None, 1=Quest, 2=MAs only, 3= < #2a, 4= ≥ #2a, 8=CG

HE _____ 0=None, 1=Quest, 2= < #3, 3= ≥ #3, 8=CG

SE _____ 0=None, 1=Quest, 2=Present, 8=CG

IRMA _____ 0=None, 1=Quest, 2=Present, 8=CG

VB _____ 0=None, 1=Quest, 2=Present, 8=CG

NVD _____ 0=None, 1=Quest, 2= < #10a, 3= > #10a, 8=CG

NVE _____ 0=None, 1=Quest, 2= < 1/2 DA, 3= > 1/2 DA, 8=CG

FP _____ 0=None, 1=Quest, 2=FPE only, 3= FPD only, 4=FPE+ FPD, 8=CG

PRH-VH _____ 0=None, 1=Quest, 2=PRH only, 3= VH only, 4=PRH+VH, 8=CG

	FIELD (0=No, 1=Quest, 2=Yes)	CENTER CIRCLE (0=No, 2=Yes)
CSME Based on HE	_____	_____
Laser Rx for CSME	_____	_____
Laser Rx for Diabetes/panret	_____	_____

Other Abnormalities?	FIELD (0=No, 1=Quest, 2=Yes)	CENTER CIRCLE (0=No, 2=Yes)
Angioid Streaks	____	____
Chorioret Abnorm/other	____	____
Br/Cent Artery Occlus	____	____
Br/Cent Vein Occlus	____	____
Arteriolar changes	____	____
Significant A/V Nicking	____	____
Hollenhorst Plaque	____	____
Asteroid Hyalosis	____	____
Nevus	____	____
Surface Wrinkling Ret	____	____
Histoplasmosis (POHS)	____	____
Retinal detachment	____	____
Laser Rx /Other	____	____
Pseudovitelleform	____	____
Macular hole/pseudohole	____	____
Myopic degeneration	____	____
Glial/cellophane	____	____
Retinal dystrophies	____	____

Other (list in comments): _____

Rev. 8 (3/31/92)

NHANES FUNDUS PHOTOGRAPH GRADING PROTOCOL

INTRODUCTION

Fundus photographs will be used in NHANES III to assess the presence of diabetic retinopathy, age-related maculopathy, and other retinal diseases. The grading system used for classifying diabetic retinopathy is based on an alternative method of grading using a modification of the Airlie House Classification Scheme; and for age-related maculopathy, a modification of the grading and classification system used in the Beaver Dam Eye Study and the Framingham Eye Study has been used.

MATERIALS USED IN GRADING

Graders will use:

a) Donaldson viewer;
b) Logan #1055 light board, modified to hold two 14 watt "daylight" fluorescent tubes;
c) Field definition grid;
d) Two standard grids: Grid A for delineating arcade area (5500μ diameter) and central circle area (1500μ diameter); and Grid B for defining macula area (3000μ diameter);
e) Standard circles for grading drusen area: C_0=63μ diameter, C_2=250μ diameter, O_2=640 μ diameter;
f) Single fundus photo, mounted in plastic sheets, taken with a Canon CR4-45NM non-mydriatic fundus camera incorporating an infrared video camera;
g) "Minified" 45° ETDRS photographic standards #2A, 3, and 10A.

GRADING PROCEDURES

A single photograph is available for each participant. This photograph will usually be graded by one grader in a masked fashion. Up to ten photographs will be mounted on each plastic sheet.

Graders began NHANES III using a paper form. By Stand 139, graders used a custom direct entry grading system. This system eliminated the need for double entry paper forms and potential transcription errors. Included in this direct entry system are consistency guidelines for ID and grading information.

The grader enters identification information: an ID # (consisting of a leading "1", a two digit stand number, and a four digit participant code); Reading List #; whether the eye is a right eye, code "0" or left eye, code "1" or a "~" in a can't grade situation.

QUALITY GRADING

FUNDUS (Item 1020):

If a fundus photograph is present, the grade is 'Present', code "2"; if the fundus photograph is not present, the grade is 'Absent', code "0", STOP. When a photo is present, but the fundus is entirely obscured the fundus is graded as 'Absent', code "0". For instance, if there is no fundus detail visible and it is impossible to judge whether the fundus photograph is of a right or left eye, the photograph is considered absent. However, if any fundus detail is discernable and/or there is even a suggestion of a lesion, the grade is 'Present', code "2", and the proceeding items should be answered until another stop condition is met.

FOCUS (Item 1030):

Focus refers to the clarity of retinal image. Because of the importance of detecting lesions in the macular area, the grader is to consider focus in 75% or more of the macula area as defined by the 3000μ diameter circle of grid B.

If retinal vessels are sharply defined or slightly fuzzy and small lesions, such as retinal microaneurysms and small drusen are visible, the grade is 'Good/Fair', or code "0". If clarity is decreased so that small retinal lesions might be missed but larger lesions, such as geographic atrophy, can be seen, the grade is 'Borderline', or code "1". If there is a pronounced decrease in sharpness, where detail of larger lesions cannot be recognized, the grade is 'Poor', or code "2".

FIELD DEFINITION (Item 1041):

The photograph is positioned on the field definition grid. A fundus photograph with the optic disc positioned entirely within the dotted line of the grid is considered 'Good', code "0". The grader proceeds to Item 1050. A fundus photograph with any portion of the optic disc positioned between the dotted line and the solid line is considered 'Fair', code "1". A fundus photograph with any portion of the optic nerve positioned outside the solid line on the grid is considered 'Poor', code "2". A photograph with either 'Fair' or 'Poor' field definition is further defined in terms of Horizontal/Vertical Field Definition in Items 1046 and 1047.

FIELD DEFINITION HORIZONTAL (Item 1046):

If the entire optic disc is within the dotted line of the grid, so that all of the optic disc, the macula and temporal retina are visible, the grade is 'Good', code "0". If any portion of the temporal edge of the optic disc is outside the dotted line of the grid, the grade is 'Temporal', code "1". If any portion of the nasal edge of the optic disc is outside the dotted line of the grid, the grade is 'Nasal', code "2". If horizontal field definition cannot be determined, the grade is 'CG', code "8".

FIELD DEFINITION VERTICAL (Item 1047):

If the optic disc is entirely located within the dotted line of the grid, the grade is 'Good', code "0". If any portion of the superior edge of the optic disc is outside the dotted line of the grid (that is, the vertical orientation is "high") the grade is 'High', code "1". If any portion of the inferior edge of the optic disc is outside the dotted line of the grid, (that is, the vertical orientation is "low") the grade is 'Low', code "2". If the vertical field definition cannot be assessed, the grade is 'CG', code "8".

ARTIFACT PRESENT (Item 1050):

If there is no artifact present, the grade is 'No', code "0". Proceed to Item 1060. If there is an artifact present, the grade is 'Yes', code "2", and the specific artifact(s) is/are checked in the appropriate item as:

Haze (Item 1051)

a green/white halo or partial halo, or a green/white cast throughout the photograph, see NHANES artifact examples;

Dust (Item 1052)

see NHANES artifact examples;

Lashes (Item 1053)

see NHANES artifact examples;

Arc (Item 1054)

a sharp edged band on the edge of the field ranging in color from white to orange, often blue tinged, usually extending no more than 180 degrees. See NHANES artifact examples;

Uneven Illumination, Center (Item 1055)

see NHANES artifact examples;

Uneven Illumination Edge (Item 1056)

see NHANES Standard #7B;

Central Dot Artifact (Item 1057)

see NHANES Standard #8;

Other (Item 1059)

if 'Other' is noted, describe the artifact in Comment section, Item 1270.

Gradability (Item 1060):

If the whole field can be graded, the grade is code "0". If the disc cannot be graded, but it is possible to grade the macula, the grade is code "1", 'Disc ungradable'. If a portion of the macula $\geq 0_2$ and less than 75% of macula (3000 diameter μ, Grid B) cannot be graded, but the disc is gradable, the grade is code "2", 'Portion macula ungradable'. If $\geq$ 75% of the macula area (3000 diameter μ, Grid B) is in 'Poor' focus, or is missing, or is obscured by a retinal hemorrhage, vitreous hemorrhage, asteroid hyalosis or some other condition and no lesion of any type is seen, but it is possible to grade the disc, the grade is code "3", 'Macula ungradable'. However, if any lesion is questionably present or present in the remaining 25% of the macula, the photo is graded and the appropriate gradability is chosen (either code "2" or code "4"). If a portion of the disc and the macula are ungradable, the grade is code "4". If neither the disc nor the macula can be graded, but other portions of the eye are visible, the grade is code "5". If none of the field can be graded, the grade is code "6". If code "6" is chosen, STOP.

FUNDUS GRADING

DIABETIC RETINOPATHY SUB-SECTION (Items 1070-1160)

LEVEL	Description
10	No diabetic retinopathy visible. No other lesions that could be mistaken for diabetic retinopathy. Items 1080 - 1160 should be marked 'None', code "0". Proceed to Item 1170 (Abnormalities).
11	Questionable diabetic retinopathy visible, usually one questionable microaneurysm (MA). Especially useful with non-mydriatic or monocular 45 degree fields as very small MA's may be difficult to discern in these photographs.
12	Retinopathy that is non-diabetic in nature but could be mistaken as diabetic or should be noted in the lesion list (hard exudate from a SSR/RPE detachment, hemorrhages and/or microaneurysms (HMA) and or intra-retinal microvascular abnormalities (IRMAs) from a branch vein occlusion). Many, not all, of the abnormalities from the global "Other" list would constitute a level 12 in the absence of other diabetic retinopathy.
14	Any combination of definite hard exudate (HE), soft exudate (SE), IRMA and/or venous loops in the absence of MA's.
15	Retinal hemorrhage present without any definite MA's.
20	MA's only with no other diabetic lesions present.
31	MA's and one or more of the following: HMA <2A, HE, venous loops, Q SE, Q IRMA, Q venous beading (VB).
41	MA's and one or more of the following: SE, IRMA.
51	MA's and one or more of the following: VB, HMA ≥2A.
60	Fibrous proliferation (FP) only, with no other proliferative lesions.
65	Proliferative diabetic retinopathy (PDR) < high risk characteristics (HRC). That is, new vessels on or within 1 DD of disc (NVD) less than standard 10A, and/or new vessels present elsewhere (NVE), and/or preretinal or vitreous hemorrhage (PRH, VH) but not meeting definition for level 70.
70	PDR ≥ HRC : NVD ≥ 10A; or NVD < 10A plus VH or PRH; or NVE ≥ 1/2 DA plus VH or PRH.
80	Total VH. Cannot grade the fundus through the VH haze.
88	Cannot assign an accurate retinopathy level, usually due to poor photo quality. While the level may be 88 some lesions may be gradable.

Once a diabetic level is chosen, all diabetic lesions questions (Items 1080 to 1160) are graded according to ETDRS protocol (see chapter 18).

In the situation where 75% or more of the macula, using Grid B, is in poor focus, and there are no diabetic lesions seen in the remaining 25%, the diabetic level cannot be less than Level 41.

OTHER ABNORMALITIES (Item 1170):

If there are no retinal or vitreal abnormalities present, the grade is 'No', code "0". The grader answers code "0" to Items 1172-1221 and proceeds to Item 1228 (Drusen Section). If there are abnormalities or photocoagulation treatment scars present or questionably present, the grade is 'Yes', code "2". If code "2" is chosen, the specific lesion(s) is (are) noted from the list that follows (Items 1172-1221) as: code "0", not present; code "1", questionably present-that is, when the grader thinks the likelihood that the lesion is present is in the 50% to 90% range; or code "2", definitely present. If 'Questionable', code "1", or 'Yes', code "2", is chosen the grader considers whether the lesion/condition is present or questionably present within the entire field, and present or not present within the central circle (CC) of Grid A, where applicable.

RPE Degeneration (Item 1172, Item 1173-Center Circle [CC])

Degeneration of retinal pigment epithelium characterized by faint greyish-yellow or pinkish-yellow areas of varying density and configuration without sharply defined borders. Hyperpigmentation is frequently seen over and adjacent to these areas. (NHANES Abnormalities Example #1).

Geographic Atrophy (Item 1174, Item 1175-CC)

Sharply defined area of drop-out of retinal pigment epithelium and choriocapillaries, exposing choroidal vessels. (NHANES Abnormalities Example #2).

Sub-retinal Hemorrhage (Item 1176, Item 1177-CC)

Hemorrhage below the retinal surface which may appear as a dark red,dark grey or greenish area. (NHANES Abnormalities Example #3).

Sub-retinal Fibrous Scar (Item 1178, Item 1179-CC)

Sheets or mounds of "white" material appearing like a scar, involving the retina. (NHANES Abnormalities Example #4).

SSR Detachment (Item 1180, Item 1181-CC)

Clear or solid, dome shaped fluid filled elevation indicating a serous or retinal pigment epithelium detachment of the retina. (NHANES Abnormalities Example #5).

Hyperpigmentation (Item 1182, Item 1183-CC)

Deposition of granules or clumps of grey or black pigment in or beneath the retina. (NHANES Abnormalities Example #6).

Chorioretinal Abnormalities/Other (Item 1184, Item 1185-CC)

Retinal and/or choroidal degeneration, regardless of cause which does not appear to be associated with age-related maculopathy.

Peripapillary Atrophy (Item 1186)

Choroidal atrophic area around disc, ≥1/2 of circumference of disc; less than 1/2 of disc circumference are considered scleral crescents and are not considered peripapillary atrophy.

Branch/Central Artery Occlusion (Item 1188, Item 1189-CC)

Obstruction of a branch or central retinal arteriole. If "fresh", may be associated with large grayish-white area of retinal infarction.

Branch Vein Occlusion (Item 1190, Item 1191-CC)

Obstruction of a branch retinal venule. A fresh occlusion is distinguished by dilated retinal venules and diffuse retinal hemorrhages. An older occlusion may demonstrate sheathed venules and retinal collateral vessels. The occluded vessel may not always be obvious.

Central Vein Occlusion (Item 1192, Item 1193-CC)

Obstruction of a central retinal venule. A fresh occlusion is distinguished by dilated retinal venules and diffuse retinal hemorrhages. An older occlusion may demonstrate sheathed venules and retinal collateral vessels.

Significant A/V Nicking (Item 1194)

Constriction of calibre of the venule at the arteriolar crossing. To determine, should be at least 1 disc diameter from disc, and should be ≥ NHANES Abnormalities Example #7.

Hollenhorst Plaque (Item 1196, Item 1197-CC)

Cholesterol emboli. These highly refractile to smudgy white lesions lie within arterioles.

Asteroid Hyalosis (Item 1198, Item 1199-CC)

Multiple spherical and stellate opacities in the vitreous. May be difficult to differentiate in nonstereoscopic photographs, should appear in front of vessels and disc. Care must be taken to differentiate from retinal drusen. If asteroid is dense, may prevent grading drusen.

Nevus (Item 1200, Item 1201-CC)

Localized increase in number of pigment bearing cells of the choroid, usually in a round or oval shape. Lack of stereopsis will make it difficult to differentiate from raised lesion (melanoma). May have drusen overlying the lesion. Should be distinguished from "bear tracks" and other hyperpigmentation of the retinal pigment epithelium if possible.

Surface Wrinkling Retinopathy (Item 1202, Item 1203-CC)

Slight contraction of thin membrane on inner surface of retina. A patch or patches of irregular increased reflection from the inner surface of retina (cellophane reflex) which may be associated with fine traction lines and vascular tortuosity. (NHANES Abnormalities Example #8).

Abnormal Disc (Item 1204)

Any unusual feature of the optic disc, such as: notching, optic nerve drusen, congenital abnormalities. If there is an 'Abnormal Disc', it should be detailed in the Comment Section (Item 1270).

Large C/D Ratio (Item 1205)

If the cup to disc ratio is .6, "Q" is marked and the ratio is noted in the Comments section. If the C/D ratio is >.6, "Yes", is chosen and the C/D ratio is noted in the Comment Section (Item 1270).

Histoplasmosis (POHS) (Item 1206, Item 1207-CC)

Presumed ocular histoplasmosis syndrome is characterized by one or more of the following: multiple peripheral atrophic "punched out" chorioretinal scars; peripapillary chorioretinal scarring; and/or macular subretinal fibrous scar. If the latter is present without other signs of POHS, code only Item 1178 (Sub-retinal Fibrous Scar) as code "2".

CSME (Item 1208)

Clinically significant macular edema is defined as either (1) retinal thickening at least 1 DA in extent, part of which is within 1 DD of the center of the macula, or (2) retinal thickening or hard exudates adjacent to thickened retina, extending to within 500 μ of the center of the macula.

Retinal Detachment (Item 1210, Item 1211-CC)

A condition in which the inner layers of the retina are pulled/separated from the pigment layer.

Photocoagulation Treatment in Arcades (Item 1212)

Focal, local or grid treatment within venous arcades as manifest by "Photocoagulation scars". This may be difficult to distinguish from focal pigmented scars.

Photocoagulation Treatment outside Arcades (Item 1214)

Scatter or local scarring from treatment outside arcades.

Other (Item 1220, Item 1221-CC)

Detail in Comment Section (Item 1270).

Any Drusen Present (Item 1228)

In order to assess further information about drusen, the grader must first answer the gatekeeper question code "2". If the eye can be graded and there are no drusen present within the field the grade is 'No', code "0". Code "0" is entered for Items 1230-1266, proceed to Item 1270 (Comment Section).

If a drusen is present or questionably present anywhere in the field or there are some, but not all, items which should be listed as CG, code "8", the grade is 'Yes', code "2". Answer Items 1230-1266.

If it is impossible to assess whether a hard or soft drusen is present in 75% of the macula, using Grid B, 3000 μ diameter, and no drusen are present in the remaining 25% of the area, the grade is 'Can't Grade', code "8". In the situation where it is impossible to grade for hard drusen, but the grader is able to assess the presence or absence of soft drusen, a grade of 'Yes', code "2", is chosen. The grader should answer the hard drusen question (Item 1230) "8" and consider the area questions (Items 1250-1264) as only referring to soft drusen.

Hard Drusen Present (Item 1230)

If there are no hard, punctate retinal drusen present, the grade is code "0" and the grader goes on to Item 1240. If the grader is from 50% to 90% certain that there are hard drusen present, that is, small, punctate drusen, the grade is 'Questionable', code "1". If there are definite hard drusen present anywhere in the field, the grade is 'Yes', code "2". If ≥ 75% of the photograph cannot be graded, and no hard drusen are seen, the grade is 'CG', code "8".

Soft Drusen Present (Item 1240)

If no soft drusen are present, that is, large drusen with distinct or indistinct margins, the grade is 'None', code "0". If the grader is between 50% to 90% certain there are soft drusen present anywhere in the photograph, the grade is 'Questionable', code "1". If the grader sees definite soft drusen anywhere in the photograph, the grade is 'Yes', code "2". If ≥ 75% of the photograph cannot be graded, and no soft drusen are seen, the grade is 'CG', code "8".

Area within Grid (Item 1250)

The grader centers the fovea in the central circle area of Grid A which is mounted on the light board. The outer edge of this grid approximately delineates the area of the major venous arcades. If there are no drusen present within this grid, the grade is 'None', code "0". If 'hard' and/or 'soft' drusen are definitely present within the grid, the grader mentally moves together all drusen present, and compares this area to a set of Standard Open Circles: Standard Circle C_0=63 μ diameter; Standard Circle C_2=250 μ diameter; Standard Circle O_2=500 μ diameter. The grader does not include 'Questionable' drusen in area estimates. If the total area of definite drusen within the grid is < Std. C_0, the grade is code "1". If the total area of drusen within the grid is < Std. C_2, the grade is code "2". If the total area of drusen within the grid is < Std. O_2, the grade is code "3". If the total area of drusen within the grid is ≥ Std. O_2, the grade is code "4". If the area within the grid cannot be assessed, the grade is 'CG', code "8".

Area Outside the Grid (Item 1260)

The grader again looks at Grid A centered on the fovea. If there are no drusen present outside this grid, the grade is 'None', code "0". If definite 'hard and/or 'soft' drusen are present outside the grid, the grader again compares the total area outside the grid with the set of Standard Open Circles. 'Questionable' drusen are not included in estimates of area. If the total area of definite drusen outside the grid is < Std. C_0, the grade is code "1". If the total drusen area outside the grid is < Std. C_2, the grade is code "2". If the total drusen area outside the grid is < Std. O_2, the grade is code "3". If the total drusen area outside the grid is ≥ Std. O_2, the grade is code "4". If the drusen area outside the grid cannot be assessed, the grade is 'CG', code "8".

Central Circle Area (Item 1262)

If no drusen are present within the central circle area of Grid A, mark 'None', code "0". If the total area of drusen within the central circle of the grid is: $<C_0$, the grade is code "1"; $<C_2$, the grade is code "2"; $<O_2$, the grade is code "3"; $\geq O_2$, the grade is code "4". If 75% or more of the central circle area of Grid A cannot be graded, and nothing is present in the remaining 25%, the grade is 'Can't Grade', code "8".

Inner Circle Area (Item 1264)

If no drusen are present within the inner area, that is, between the central circle boundary and the outer edge of the grid, the grader chooses 'None', code "0". If the total area of drusen within the inner area of the grid is: $<C_0$, the grade is code "1"; $<C_2$, the grade is code "2"; $<O_2$, the grade is code "3"; $\geq O_2$, the grade is code "4". If 75% or more of the inner area of Grid A cannot be graded, and no drusen are present in the remaining 25%, the grade is 'CG', code "8".

Central Circle-Soft Drusen Present (Item 1266)

If there are no soft drusen present within the central circle area of the grid, the grade is 'None', code "0". If soft drusen are questionably present in this area of the grid, that is, the grader thinks the likelihood of presence of soft drusen is between 50-90%, the grade is 'Q', code "1". If soft drusen are definitely present in the central circle area the grade is 'Yes', code "2". If 75% or more of the central circle area using Grid A cannot be graded, and the grader does not see soft drusen in the remaining 25%, the grade is 'CG', code "8".

Comments (Item 1270)

A comment is necessary if: In Item 1050) Artifact Present, 'Other' is chosen; In Item 1170) Abnormalities..1202) 'Abnormal Disc' and/or 1214) 'Other' is/are chosen. A comment may be noted for any other unusual feature found.

SOF-ES GRADING PROTOCOL

1.0 OVERVIEW

The SOF-ES cataract grading protocol is an adaptation of the AREDS lens opacity grading protocol, which is an adaptation of the Wisconsin System for Classification of Cataracts from Photographs[1].

A single nonstereoscopic photograph taken with a modified Topcon slit lamp camera according to a specified protocol is used to grade nuclear sclerosis and nuclear color. Degree of nuclear sclerosis is graded by comparing the photograph with a series of six standard photographs. Both the interval into which the photograph being assessed falls and its approximate position within that interval are estimated. The principal characteristics evaluated are the optical density of the nucleus and the clarity of its normal landmarks (Sections 2.2 and 2.3). Nuclear color is graded on a four-step scale by comparing the color of the specular reflection near the posterior surface of the lens in the photograph being assessed with the comparable feature in a series of three standard photographs (Section 2.4).

Two nonstereoscopic photographs taken with a modified Marcher retro-illumination camera according to a specified protocol are used to estimate the extent of cortical and posterior subcapsular lens opacities and to record the presence of other opacities. A grid superimposed on the photographs divides the dilated pupil into 17 subfields, so that the area of each occupied by opacity can be estimated (Sections 3 and 4). The area within a 5 mm diameter circle (the "central zone", comprising 9 of the subfields) is considered of primary importance, since it is expected that pupillary dilation to at least this degree will be achieved in most SOF participants, and it is this central zone that mostly affects vision.

A nonstereoscopic photograph of the red reflex taken with the Canon fundus camera according to a specified protocol is used to assist grading of the Marcher photographs and to recognize opacities not visible in them. This photograph (albeit taken through a dilated pupil) is also used to grade degree of iris pigmentation (iris color) on a four-step scale, by comparison with three standard photographs (Section 5).

The results of the grading are recorded on the SOF-ES Lens Grading Form, (Exhibit 1). The form includes a section for comments where it is possible to record unusual, presumably non-age-related lens opacities. The grading grid is illustrated in Exhibit 2. The standard photographs are on file at the Jules Stein Eye Institute Reading Center, 100 Stein Plaza, Los Angeles, CA 90095-7004 and the Wisconsin Reading Center, P.O. Box 5240, Madison, Wisconsin 53705.

2.0 SLIT LAMP PHOTOGRAPHS

2.1 Camera features and artifacts

The Topcon Model SL-6E photo slit lamp camera has been modified so that the angle between the illumination beam and the observation system, the beam width and intensity, and the magnification remain the same for all cameras for all subjects. Fixation targets have been added (viewed with the eye being photographed) so that the path of the slit beam through the lens is the same for right and left eyes (the beam is to the examiner's left of the observation system, for both right and left eyes, so that the posterior surface of the lens is always to the observer's right). A detailed protocol is specified, including focusing of the camera at the center of the lens nucleus. Two (nonstereoscopic) slit lamp photographs of the lens are mounted in a plastic sheet along with the fundus, red reflex, and retro-illumination photographs for that eye.

2.2 Slit lamp appearance of the lens and definitions

As the slit lamp beam transverses the normal adult lens, differences in refractive indices result in alternating brighter and darker bands of varying widths (See SL Standard Photograph 1). Because the depth of focus in the photographs is fairly shallow, these bands become less well defined the farther they are from the center of the lens, the ideal focal point of the camera. In SL Standard 1 a wide dark band can be seen running vertically through the center of the lens. This is termed the *central dark interval*[2] or the *sulcus* of the nucleus (and corresponds to the *embryonal nucleus).* Bordering the sulcus anteriorly and posteriorly are two broad, short, bright bands. The surfaces of these bands facing the sulcus tend to be flat or only slightly curved, while the surfaces facing the lens capsule are more steeply curved. In SL Standard 1 the posterior of these two bright bands is rather steeply curved both posteriorly and anteriorly, i.e., is bean-shaped. This is a common appearance and has led to the use of the descriptive term *lentils* for these bright bands, which are part of the fetal nucleus. The anterior and posterior Y-sutures can sometimes be seen in the anterior and posterior lentils. They are not clearly visible in SL Standard 1, but part of the posterior suture can be seen in SL Standard 3.

There are differences in interpretation regarding the remaining bands between the lentils and the lens capsule. According to Berliner[2] the bright bands immediately external to the lentils, visible as narrow, tall, relucent bands with dark bands of equal or slightly narrower width adjacent to them, represent the anterior and posterior surfaces of the lens at birth, the "fetal nucleus'. In the Oxford System, these bands are described as the anterior and posterior limits of "the nucleus"[3]. In our grading system these bands will be referred to as the anterior and posterior *nuclear surface bands.* That part of the lens between (and including) these bands is considered the *nucleus* and is the only part of the lens evaluated in the slit lamp photographs. The term *nuclear landmarks* will be used to refer to all the parts of the nucleus described above, i.e., the sulcus, the lentils, the nuclear surface bands, and the dark bands between the lentils and the nuclear surface bands.

In SL Standard 1, three additional bright bands are visible: (1) a broad one at the posterior surface of the lens, (2) a narrower one at the anterior surface of the lens, and (3) another relatively narrow one between the anterior surface of the lens and the anterior nuclear surface band. The third of these bands is considered by Berliner to represent the anterior surface of the "adolescent" or "adult" nucleus; in the Oxford System it is considered to be part of the lens cortex. In SL Standard 1 the reflection of the slit beam from this band and from the posterior lens surface is particularly bright ("specular reflection"). The anterior chamber lies between the surface of the anterior capsule and the wide steeply curved band of the cornea. The downward pointing arrow that appears to be within the anterior chamber is a reflex from a mirror in the slit illumination system and ideally should fall midway between the anterior surface of the lens and the posterior surface of the cornea, as it does here.

2.3 Grading nuclear sclerosis

2.3.1 Characteristics graded

In grading the severity of nuclear sclerosis two factors are considered: (1) the optical density (perceived as brightness or relucency, sometimes described as "opalescence") of the nuclear landmarks, especially the sulcus, and (2) the definition of these structures (contrast between the bright and dark bands). Optical density is given greater weight, in part because it is less influenced by suboptimal focus than is definition of nuclear landmarks. In the early stage of sclerosis, increased optical density is noticeable only in the normally dark bands, particularly the sulcus (see SL Standards 2, 3, and 4), but in advanced stages the density of all bands becomes greater (see SL Standards 5, 6 and 7). With increasing nuclear sclerosis, the definition of nuclear landmarks decreases, and finally disappears.

When the focus of the photograph being graded is too anterior, posterior landmarks will be blurred, and vice versa. In judging the definition of landmarks in such cases, primary emphasis should be placed on the part of the lens that is in better focus. The optical density of the sulcus also may appear to increase as the plane of focus moves farther from it, but it is difficult for the grader to make any allowance for this, and no such attempt should be made. "Cannot grade" may be assigned in extreme cases of incorrect focus (see Section 2-6).

2.3.2 The grading scale

The grader compares the photograph being graded with seven standard photographs, which show progressively increasing severity of nuclear sclerosis (SL Standards 1-6). The grader first determines the interval between adjacent standards into which the photograph being graded falls and then estimates its position in the interval to the nearest **half**. For example, if the lens being graded is considered to have nuclear sclerosis only slightly more severe than that in SL Standard 2, the grade 2.0 is assigned; if half way between SL Standards 2 and 3, the grade 2.5 is assigned. **Photographs with less optical density and greater definition of landmarks than Standard 1 (virtually a normal lens) are assigned the grade 0.5; those with nuclear sclerosis exceeding that of SL Standard 6 are assigned the grade 6.5.**

2.3.3 Description of slit lamp standard photographs

To be comprehensive, this description of standard photographs includes a description of the Y-sutures. However, their status is ignored in judging definition of the lentils. Not only is visibility of the sutures highly vulnerable to changes in the plane of focus, but they may in fact become more distinct as the relucency of the lentils increases (i.e., with the onset of mild sclerosis).

In **SL Standard 1** the nuclear landmarks are easily identified. The sulcus is well defined and appears dark throughout the vertical extent of the nucleus. (The small circular red dot on the anterior edge of the sulcus is a reflection of the fixation target.) The density of the posterior lentil is greater than that of the anterior, and its edges are more clearly defined. The Y-sutures are not visible in this photograph, except perhaps for a faint line centrally in the posterior lentil. the anterior and posterior nuclear surface bands and the narrow dark hands bordering them are easily discerned. As one would expect because of their distance from the point of focus, the remaining bright bands are out of focus.

In **SL Standard 2** the sulcus is denser (or more relucent, thus less black) and is less well defined, particularly superiorly and inferiorly. Although the anterior and posterior nuclear surface bands are still well defined, the dark bands between them and the lentils are denser.

In **SL Standard 3** the density of all the dark bands has increased, leading to a decrease in distinctness of the of the landmarks. The density of the sulcus has increased to the point that its definition has been lost, except for its central one-third. The anterior nuclear surface band cannot be distinguished at all, except perhaps centrally. The posterior nuclear surface band can only be distinguished centrally. The anterior lentil has become denser. Part of the posterior Y-suture is easily identified in the posterior lentil.

In **SL Standard 4** there appears to have been a further increase in the density of the dark bands. Only a suggestion of the sulcus can be detected. Towards the upper and lower ends of the sulcus segments of what appears to be the equator of the fetal nucleus (or a zone just beneath its surface) are visible as steeply curved white lines. Only a small part of the anterior lentil is visible. The posterior nuclear surface band cannot be seen at all and the anterior one is very faint.

In **SL Standard 5** there has been a further increase in density of both the dark and bright bands. A very faint shadow centrally marks the sulcus; the normally dark bands separating the nuclear surface bands from the lentils have increased in density to equal the increased density of the remaining nucleus. Only the dark hands external to the nuclear surface bands are well defined, and these are not included in the assessment of nuclear opacity.

In **SL Standard 6** there has been a further increase in density of both dark and bright bands. The sulcus and lentils cannot be distinguished and the density of the area assessed is greater than that in SL Standard 5.

In **SL Standard 7,** nuclear landmarks are indistinguishable due to increased density, which in the area assessed is even greater than that in SL Standard 6 (This is a fake image and is not an image of a real lens). We will not use this standard in our grading.

SL Standard 8 is used only in grading lens color (see below). Its grade for nuclear sclerosis would be near the lower end of the 4.0-4.9 range, because the optical density of the nucleus is a little greater than that of SL Standard 4 (although nuclear landmarks are better defined).

2.4 Grading lens color

2.4.1 Characteristics graded

In most adults, the gray-blue nucleus typical of youth begins to yellow with increasing age, although there is great variation in the age at which this begins. Yellowing may not develop at the same rate in both eyes of an individual and in rare cases may appear in only one eye[2]. The color may continue to deepen and intensify, turning from pale yellow to gold to orange and finally to brown ("brunescent"). In rare cases the nucleus may appear nearly black in color. The greatest intensity of the color change is seen in the specular reflection from the central zone of the posterior surface of the lens. It is at this point that the grader should assess the color, comparing it with the same area in the standard photographs.

2.4.2 The grading scale and descriptions of standard photographs

Slit lamp Standard Photographs 2, 4, and 8 are used as standards for grading lens color. The grader compares the photographs to standards both with and without the Larson stereo viewer. Sometimes subtle changes in color can be perceived more easily without the stereo viewer. The standards for lens color and their use in grading are described below.

In **SL Standard 2** slight yellowing can be seen at the posterior surface of the lens and extending forward into the posterior part of the nucleus. This is best appreciated by comparison with SL Standard 1, in which there is no yellowing. If color in the photograph being graded is less yellow than that in SL Standard 2, the grade is 1; for yellowing $\geq$ SL Standard 2 but $<$ SL Standard 4 the grade is 2.

In **SL Standard 4** a broad, bright, pale yellow reflex can be seen at the posterior pole of the lens. If yellowing in the photograph being graded equals or exceeds that in SL Standard 4 (but $<$ SL Standard 8), the grade is 3. SL Standard 3 provides an example of yellowing very nearly the same as that in SL Standard 4, but with less specular reflection. For example in SL Standard 5 color is slightly more yellow than in SL Standard 4 and would receive the grade 3.

In **SL Standard 8** the reflex from the posterior pole of the lens has a deeper yellow color than that in SL Standards 3 or 4. If color in the photograph being graded is as yellow as or more

yellow than that in SL Standard 8, the grade is 4. To illustrate, in SL Standard 6 color is substantially more yellow than in SL Standard 8 and would receive the grade 4.

If lens color cannot be graded the grade is 8.

2.5 Cortical flecks

Small, discrete white flecks or dots are often visible in the peripheral cortex of the lens in the slit lamp photograph. Although such opacities occur commonly with some systemic (metabolic) diseases, they are also often found in healthy individuals. The relationship of cortical flecks to other age-related changes is unclear. These small snowflake-like opacities may be found scattered throughout the lens periphery, but are most often seen, in photographs taken according to the SOF-ES protocol, at the superior and inferior poles of the cortex. Their presence or absence is recorded for the lens as a whole.

2.6 Gradeability of slit-lamp photographs (use of "cannot grade")

Three factors determine gradeability of slit-lamp photographs: focus, placement of the slit beam, and area of the lens visible (determined by pupil size and position of the eyelids). The depth of focus of the slit lamp camera is shallow (1 – 2 mm), but broad enough so that the entire thickness of the nucleus can be in satisfactory focus simultaneously when the plane of focus is in the sulcus. If the plane of focus is at or anterior to the anterior lens capsule in the optic axis, or at or posterior to the posterior capsule in the optic axis, photo quality is graded inadequate (see 8.3.4.1). However, if such photographs are presented to the grader, a grade is assigned if possible.

If the slit beam is displaced laterally so that an imaginary vertical line through the sulcus does not fall between vertical lines that would cross the pupil margin from 10:30 to 7:30 and from 1:30 to 4:30, too little of the nucleus will be visible to allow grading. Similarly, if a small pupil or drooping upper lid allows less than one-half of the vertical extent of the nucleus to be seen, cannot grade is assigned.

3.0 MARCHER RETRO-ILLUMINATION PHOTOGRAPHS

3.1 Camera features and artifacts

Because the illuminating and viewing axes of the Marcher camera coincide, the image it records is provided by light reflected from the fundus. This image is reddish-orange because of pigment in the retinal pigment epithelium and choroid, and because of blood in the choroidal, and to a lesser extent the retinal vessels. Lens opacities (other than nuclear sclerosis) are visible as dark spots because they partially or completely block the light reflected from the fundus behind them (retro-illumination). Two nonstereoscopic color photographs are taken with the Marcher camera through the dilated pupil, one focused on the iris (corresponding to the anterior cortex of the lens) and one focused 3-5mm more posteriorly (at or near the posterior capsule).

To reduce the bright reflection from the cornea of the Marcher camera's flash, polarizing filters are placed (at opposite axes) in front of the light source and in front of the film. In the Marcher photograph there is a characteristic unevenness in color in the form of a darker orange cross, similar in shape to the central part of a celtic cross.

In the four peripheral areas not covered by the orange cross, the fundus reflex is lighter and more yellow in color. This nonuniformity is normal for the system and should not be confused with lens abnormality.

Frequently in the anterior Marcher photograph a pale white rectangular reflection from a mirror in the illuminating pathway can be seen centrally (with a longer axis vertical). A similar but fainter, out-of-focus image can be seen in many of the posteriorly focused Marcher photographs. These images should be ignored when grading.

3.2 Appearance of lens opacities in Marcher retro-illumination photographs

Lens fibers grow in concentric layers and continue to develop throughout life. Each new layer grows beneath the capsule and around the fibers internal to it pushing these fibers inward. For this reason opacities of the lens tend to be location-specific, depending on the stage of lens development at which they occur. For example, a common type of congenital cataract is confined to a zone within the nucleus ("zonular cataract").

In retro-illumination, the normal lens appears uniformly transparent. Discrete lens opacities are visible as dark interruptions of this transparency, even when their appearance in direct illumination is subtle. The principal types of age-related lens opacities assessed in the Marcher photographs are cortical and posterior subcapsular. Typical cortical opacities are wedge-shaped and oriented radially. Another appearance of cortical opacities is a collection of fine granular dots ("stippling"). This is less common. Posterior subcapsular opacities are located just beneath the posterior lens capsule. Typically they are centered at or near the posterior pole of the lens and extend for varying distances towards the lens equator. The areas involved by cortical and posterior subcapsular opacities are estimated separately for each of the 9 subdivisions of the central zone of the grading grid (within the 5 mm diameter circle). In addition, the number of cortical "vacuoles" in each of these subdivisions is counted up to a limit of 10 (excluding any that form part of a cortical spoke or a posterior subcapsular opacity and are therefore included in those estimates). Vacuoles have the appearance of small, round or oval, clear cyst-like spaces. The presence or absence of anterior cortical opacities that appear white from directly reflected light rather than black from blocking of light reflected from the fundus (white anterior cortical opacities, or WACOS) is also recorded for each of these subdivisions.

In nonstereoscopic retro-illumination photographs, artifacts can mimic lens opacities because they also block light reflected from the fundus. Common problems are debris on the cornea (such as mascara, eyelashes, or strands of mucus) and irregularities of the cornea following examination procedures (such as applanation tonometry or use of a diagnostic contact lens). A broad tear meniscus may form above the lower lid margin, appearing as a narrow blurred area in the Marcher photograph; care should be taken not to confuse this with an abnormality in the lens cortex. Many of these problems can be detected by careful scrutiny of the Canon red reflex photograph.

3.3 Grading Marcher photographs

3.3.1 Measurement of pupil diameter

The diameter of the pupil is measured from the anterior Marcher photograph using a magnifier with a built-in millimeter scale (Bausch and Lomb, 7X). Both the horizontal diameter from 9:00 to 3:00 and the vertical diameter from 12:00 to 6:00 are measured on the film and

recorded to the nearest tenth of a millimeter (these may not always be the widest and narrowest dimensions). If the pupil is particularly distorted the grader measures the horizontal and vertical meridians as specified and notes the distortion under the Comments section. Because the Marcher camera has a magnification of 2X, the film measurements will be twice the actual pupil size, that is, in an eye with a 5mm pupil the measurement on film will be 10mm.

3.3.2 Lens grading grid

In order to allow the grader to specify the location and extent of lens more precisely, a grid is used to divide the Marcher photograph into subfields. The grid has three concentric circles: a central circle with radius 2mm; an inner circle with radius 5mm and an outer circle with radius of 8mm. The outer circle is used only to facilitate placement of the grid, not to define the limits of the outer subfields, which are defined by the pupillary margin.

Equally spaced radial lines (meridians) at 10:30, 12:00, 1:30, 3:00, 4:30, 6:00, 7:30, and 9:00 o'clock divide the zones between the central and inner circles and between the inner circle and the pupillary margin into eight subfields each. The grid therefore has 17 subfields: the central subfield; eight equal inner subfields; and eight outer subfields, the areas of which vary with pupil size. On the grading form the subfields are designated as follows:

Central,
1A (10:30-12:00), 1B (12:00-1:30),
2A (1:30-3:00), 2B (3:00-4:30),
3A (4:30-6:00), 3B (6:00-7:30),
4A (7:30-9:00), 4B (9:00-10:30).

Thus for right eyes inner and outer subfields 2A and 2B are nasal, while for left eyes inner and outer subfields 4A and 4B are nasal. A diagram of the grid is provided as Exhibit 2. The central and inner subfields are referred to as the "central zone".

Short perpendicular ticks are spaced at 1mm intervals along each meridian to facilitate placement of the grid. The grid is affixed to the front of the anterior Marcher transparency so that the central circle is equidistant from the pupillary margins vertically and horizontally. Occasionally the eyelid may obscure a portion of the pupil superiorly, making placement of the grid more difficult. Despite possible interference from the lid, the best determination of the center of the pupil should be made and the grid placed accordingly. The grid should not be removed from the transparency unless the grader feels the grid has been improperly placed, in which case the grid will need to be recentered and the photograph regraded (if previously graded).

With the grid placed on the anterior photograph, both the anterior and posterior Marcher photographs are mounted side-by-side in the plastic sheet so that they can be viewed simultaneously. This allows the grader to combine lesions seen in the anterior cortex with those seen in the posterior cortex, resulting in a single grade for each type of cortical opacity. To determine whether a posterior lesion falls within a particular subfield without attaching an additional grid to the posterior photograph, both the anterior and posterior photographs are viewed simultaneously with the stereo viewer as a pair, thus allowing the grid to be visually superimposed over the posterior photograph. Another technique is to close one eye and then the other in rapid succession, so that the immediate memory of the position of the grid on the anterior photograph helps determine the location of a lesion seen in the posterior photograph.

3.3.3 Grading rules

When determining the area of each subfield involved by definite cortical or posterior subcapsular opacities, the grader records the percentage to the nearest whole number. However, when the total percentage of the subfield involved is less than one percent (for example when one or two small isolated dots are present), the grader by convention records the percentage as 0.5%.

When it cannot be determined with ≥90% certainty that the lesion being graded is indeed that lesion, but the grader is ≥50% although <90% confident of the identity of the lesion, the grade is "questionable" and is recorded in the appropriate box for that lesion as "Q". If the grader is <50%. confident, the grade is "absent," code 0. If a subfield cannot be graded, the grade is recorded as "CG" (see section 3.6)

3.4 Grading cortical lens opacities

Cortical opacities vary in shape, size, location in the pupil, and depth within the anterior and/or posterior cortex of the lens. The lesions graded are cortical opacities (spoking or stippling), vacuoles, and WACOS.

3.4.1 Cortical stokes and cortical stippling

Cortical spokes are linear or wedge-shaped radially oriented opacities that partially or completely block light reflected from the fundus. Their appearance varies from dense black solid opacity to diffuse collections of dots with intervening clear areas. They usually originate near the peripheral edge of the lens (the equator) and extend toward the center of the pupil. They are frequently broader at the base, tapering as they extend centrally. Spokes are more often seen in the anterior cortex, although they often appear in both the anterior and posterior cortex and occasionally only in the posterior cortex. Occasionally strings of vacuoles are aligned in radial spoke-like formations, these, too, are graded as cortical spokes, not as vacuoles (see section 3.4.2)

Cortical opacities may also appear as collections of uneven granular dots that do form spokes; these are referred to as stippling. Typically, in zones of stippling much of the lens between the dots is clear. Therefore, in estimating area involved by stippling the grader mentally sweeps the opacities together and estimates the area they would cover if contiguous.

When grading cortical opacities, the grader mentally combines the anterior and posterior images, then estimates and records the percentage of area in the composite image covered by opacities (spokes and stippling combined) in each subfield. Care should be taken to confirm that the opacities seen in the posterior photograph are not merely out-of-focus images of the same opacities seen anteriorly, so as not to over-estimate the area involved.

3.4.2 Vacuoles

Vacuoles appear as small round or oval, clear, cyst-like spaces with sharply defined borders. With retro-illumination some or all of the borders of a vacuole usually appear dark. Vacuoles may be found at any level in the cortex. Isolated vacuoles are counted up to a maximum of ten in each of the 9 subfields of the central zone. If vacuoles appear as part of a

cortical spoke or if their configuration is spoke-like, they are considered as spoking and are not tallied in the vacuole count. Similarly, if vacuoles appear to be part of a posterior subcapsular opacity (see section 3.5), they are considered PSC and not included in the vacuole count.

3.4.3 White anterior (and/or posterior) cortical opacities (WACOS)

In the Marcher photographs cortical opacities sometimes are seen as white or yellow-white spots of variable size and shape with hazy, ill-defined borders. WACOS are located mainly in the anterior cortex, but may be seen in both the anterior and posterior Marcher photographs. WACOS do not appear to be flat but rather to have some volume. These opacities vary greatly in number and are usually located centrally rather than peripherally. WACOS are graded in each of the 9 subfields of the central zone as being absent (0), questionably present (1), present (2) , or cannot grade (8).

Often WACOS appear as pale gray opacities in the red reflex photographs. Because of the color difference, there is a risk that the grader may fail to identify them as WACOS and erroneously indicate the presence of an opacity in the red reflex photograph not present in the Marcher Photograph (item 300 on the form). Careful comparison of the location of the appearances in the two photographs is necessary to avoid this error.

3.5 Grading of posterior subcapsular (PSC) opacities

Posterior subcapsular (PSC) lens opacities are a less frequent but visually important finding in the older population. They are usually located in the central part of the pupil, and are often accompanied by cortical opacities. PSC opacities develop in what appears to be a single layer immediately anterior to the posterior lens capsule, and thus can be in sharp focus only in the posterior Marcher photograph. Because of the camera's shallow depth-of field, if the focus is not directly on the PSC opacities, they may be somewhat out-of-focus even in the posterior photograph, but focus will still be sharper than in the anterior photograph. PSC opacities may vary from a darkly opaque network to a thin brown or gray barely discernible haze. These opacities are usually lacy in configuration, often with discrete round or oval "bubbles" or vacuoles within them. Less frequently PSC opacities may appear granular. Any vacuole touching or part of the PSC network is graded as PSC opacity and not included in the vacuole court. Usually PSC opacities have irregular edges, are asymmetrical, and are limited to the central and inner subfields. The Canon stereoscopic red reflex photograph may be helpful in determining whether a central opacity that is visible but out-of-focus in the posterior Marcher photograph is in fact a PSC opacity.

From the posterior Marcher photograph the grader estimates the percentage of the area covered by PSC opacities in each of the 9 subfields of the central zone. Because PSC opacities are fairly compact, with only a few small open areas in the lacy pattern, extent of opacity is estimated without any attempt to subtract clear spaces. Because the grid is not present on the posterior photograph, the techniques described in Section 3.3.2 (last paragraph) are recommended to determine the subfield location of PSC opacity. Care should be taken not to confuse a Mittendorf dot, a remnant of the fetal hyaloid vascular system sometimes seen on the posterior capsule, with PSC opacities (Section 4.1).

3.6 Gradeability of Marcher photographs (use of "cannot grade')

3.6.1 Anterior Marcher photograph

To grade for cortical opacities, vacuoles, and WACOS, the anterior Marcher photogragh must be present and gradeable; that is, the anterior photograph must be in reasonably good focus and at least two-thirds of the subfield being graded must be visible and free from major artifacts. Thus, if actual pupillary diameter were less than 4mm (defined by the first tick posterior to the middle circle on each meridian, 4mm radius on the grid, 2mm radius of the pupil), all inner subfields would be assigned cannot grade. When grading each of the outer subfields the procedure followed is similar to that used for grading the inner subfields, except that the total area of each subfield used as the denominator in applying the two-thirds rule is variable rather than fixed. However, if a portion of one of the outer subfields is obscured by an eyelid, it is easy to estimate the size of the portion obscured, and this is considered part of the urgradable portion in applying the two-thirds rule.

3.6.2 Posterior Marcher photograph

To grade for posterior subcapsular cataract, the posterior Marcher photograph must be present and at least the central subfield must be gradeable. The distance between the anterior and posterior surfaces of the lens varies from subject to subject, and increases with age. The protocol takes this variablility into consideration by allowing the posterior photograph to be taken from 3 to 5mm posterior to the anterior photograph. If the distance recorded by the photographer between the anterior and posterior photograph differs substantially from this range (< 2.5mm or > 6.0mm) and no PSC opacities are visible, "cannot grade" is assigned. However, if PSC appears to be present, though out of focus, the grader should attempt to grade it if at all possible, without regard to the distance recorded.

3.7 Opacities absent in the Marcher photographs but present in the Canon red reflex photograph

Occasionally opacities not apparent in the Marcher photographs can be identified in the Canon red reflex stereo photograph. One explanation is that the very shallow depth of field of the Marcher camera (approximately 1mm) does not allow opacities outside this range to be seen while the greater depth of field of the Canon camera captures them. The presence of such opacities is recorded in item 300 of the form for the lens as a whole (absent; questionable; definite, but not PSC opacity; definite PSC opacity, with or without other opacities; or cannot grade). Care should be taken not to record any gray opacities seen in the fundus reflex photograph, and identifiable as white cortical opacities in the Neitz photographs, as opacities <u>not</u> present in the Neitz photograph (see WACOS, Section 3.4.3).

In addition, because of the optics involved, a slight shift in gaze may change the perceived position of an opacity seen in the fundus reflex photograph from the position observed in the Marcher photograph, thus giving the erroneous impression of the presence of two opacities instead of one.

4.0 OTHER OPACITIES (OBSERVED IN ANY TYPE OF PHOTOGRAPH)

Other opacities are assessed for the lens as a whole.

4.1 Mittendorf dot

Infrequently, a Mittendorf dot, a remnant of the fetal hyaloid vascular system, can be seen attached to the surface of the posterior lens capsule. It is usually located slightly nasal to the center of the lens and appears as a small, round or oval, dense black dot approximately 125-350 μm in diameter. It should not be confused with PSC opacities. When a Mittendorf dot is present, the grader checks the appropriate box.

4.2 Pseudoexfoliation of the lens capsule

Occasionally pseudoexfoliation of the lens capsule, a deposit on the anterior lens capsule that has the appearance of a curling or scrolling back of a thin transparent membrane, can be seen in a circular zone inside the edge of the dilated pupil. The everting free ends of the tissue sometimes may appear to curl toward the lens equator, in strips of varying width. Pseudoexfoliation is often very subtle and easily can be missed or mistaken for cortical opacities. The origin of pseudoexfoliation is unknown, but it is sometimes associated with glaucoma. When pseudoexfoliation is present, the grader checks the appropriate box.

4.3 Miscellaneous opacities

Presence of opacities other than those described above is indicated by checking the "other" box and describing the opacities in the Comments section. There are many types of non-age-related lens opacities, which may be seen in any layer of the lens. These include polar cataracts (white or gray circular or oval opacities within the fetal nucleus which may or may not extend beyond it); stellate cataracts associated with the Y-sutures, traumatic cataracts, and cataracts of unknown origin. Vitreous opacities like asteroid bodies may also confound grading.

5.0 GRADING IRIS PIGMENTATION (COLOR) IN CANON RED REFLEX PHOTOGRAPHS

5.1 Introduction

The iris is a thin membrane separating the anterior and posterior chambers. Peripherally the iris is continuous with the ciliary body. In the undilated state, the pupillary margins rest on the surface of the lens. The iris consists of a layer of mesothelium anteriorly, a stroma made up mostly of blood vessels centrally and two layers of pigment epithelium posteriorly. Located within the stroma are melanin-containing pigment cells which vary greatly in number. The color of the iris depends mainly on the presence and number of these cells. When light passes through the translucent stroma unimpeded by stromal pigment cells, the rays of shorter wave length (blue) are reflected back preferentially, resulting in a blue-appearing iris. (2) This phenomenon is analogous to the sky appearing blue due to scattering (diffraction) of light as it passes through atmospheric haze. As the melanin-containing pigment cells in the stroma increase in number, the iris color changes from blue to various shades and combinations of blue, green, yellow and brown.

In the lightly-pigmented iris the radial, thick-walled, opaque iris blood vessels are well defined, appearing as slightly curving white lines that run from the periphery of the iris to within about 1mm of the pupillary margin, where they end by joining a circular vessel at the

"collarette". Between the collarette and the pupil margin, the color of the iris often appears darker, in part because the stroma is thinner, allowing the dark color of the pigment epithelium to be seen more clearly, and in part because of the black fringe of pigment epithelium that is directly visible at the pupil margin (see Iris Standard Photograph 1, with undilated pupil). The zone of iris between the collarette and the pupil margin is called the pupillary zone to distinguish it from the remainder of the iris, called the ciliary zone. When the pupil is dilated the pupillary zone is pulled partially under the ciliary zone, so that it appears narrower and is often in partial shadow (see Iris Standard Photograph 1, with dilated pupil). When grading iris pigmentation the pupillary zone is excluded from consideration. Also excluded are iris crypts and iris freckles (see below). The characteristic assessed is the degree of *browness* of the iris stroma, on the blue-green-yellow-light brown-dark brown continuum.

The unknown photograph to be classified was taken with the pupil dilated and is compared with a series of standard photographs, also taken with the pupil dilated.

5.2 Conditions which may confound grading

Several conditions may make it difficult to judge the density of the stromal pigmentation. A portion of the iris may be obscured (for example, when a broad arcus senilis of the cornea is present). Overall pigmentation may appear darker (blacker) because of the presence of many iris crypts, through which the dark pigment epithelium of the iris is plainly visible. Similarly, the presence of many iris freckles or nevi may give the impression of a browner iris. These conditions, described below, should be ignored when assessing iris pigmentation.

Arcus senilis, an aggregate of lipid material ringing the cornea, is seen as a white or grayish-white opaque or nearly opaque band located near the limbus and separated from it by a narrow uninvolved clear band. The opacity may involve only one or two clock hours or may encircle the cornea completely. If the opaque band is broad and completely encircles the cornea, it may make grading for iris pigmentation difficult when the pupil is dilated. The grader should select an area where the band is narrowest and grade the area between the posterior edge of the band and the collarette (or the pupil margin, if the collarette is not visible).

Iris crypts are openings or spaces in the stroma through which the dark pigment epithelium below can be seen. The blackness of the exposed pigment epithelium is <u>not</u> a consideration in the evaluation of iris pigmentaticn.

Iris freckles are isolated spots of brown or reddish brown pigment located in the superficial layers of the iris. They appear to be "thin" (as opposed to the dense or "solid" appearance of a nevus) and vary widely in shape and size. Prominent iris freckles can be seen in Iris Standard Photograph 2 (undilated pupil) at 11:30 and 5:30. At 4:30, two smaller, lighter brown freckles can be seen (almost touching one another). Near them (toward the pupil margin) is an iris crypt. All of these features can also be seen in Iris Standard Photograph 2 (pupil dilated), but less clearly. A small freckle is visible at 5:00 near the limbus in Iris Standard Photograph 3.

An **iris nevus** is a solid-appearing dark area with regular or irregular borders. Nevi are usually darker, fewer in number and appear to extend deeper into the stroma than freckles. They are thought to be composed of groups melanophores within the stroma and are benign.

5.3 Grading iris pigmentation (color)

In **Iris Standard 1** there is little or no evidence of stromal pigment. Except for a tiny freckle at 6:00 over the collarette, no brown pigmentation can be seen in the iris. The gray-white radial blood vessels are prominent when the pupil is small (i.e., in the undilated variant of Iris Standard 1), but are less distinct when it is dilated. Because of the paucity of stromal melanophores, the dark pigment epithelium beneath the stroma can be seen easily through the iris crypts (to be ignored when evaluating the degree of pigmentation present). Photographs with iris pigmentation equal to or less than that in Iris Standard 1 are graded 1. The dilated pupil versions of the Iris Standard Photographs are to be used in grading.

In **Iris Standard 2** there is an increase in pigmentation, which results in the appearance of a very faint wash of pale brown throughout the iris and leads to a muted graying of the color. The radial blood vessels are prominent (in the undilated variant) but appear more yellow-gray in color, reflecting the increase in pigmentation. The iris crypts are not as noticeable as in Iris Standard 1. The iris freckles, described above (Section 5.2) are to be ignored. Eyes with iris pigmentation greater than Standard 1, but equal to or less than Standard 2, are graded 2.

In **Iris Standard 3** there is a marked increase in pigmentation from the previous standard, giving the iris an overall appearance of a light to medium brown. Eyes with iris pigmentation greater than Standard 2, but equal to or less than Standard 3, are graded 3.

Eyes with iris pigmentation greater than Standard 3, are graded 4. Cannot grade, code 8, is assigned when iris pigmentation cannot be determined.

6.0 REFERENCES

1. Klein BEK, Magli YL, Neider, Mw, Klein, R. Wisconsin System for Classification of Cataracts from Photographs. NTIS Accession No. PB 90-138306.

2. Berliner ML: Biomicroscopy of the eye: Slit lamp microscopy of the living eye. Vol II, New York, Harper & Bros, 1949.

3. Sparrow TM, Bron AJ, Brown NAP, Ayliffe W, Hill AR: The Oxford Clinical Cataract Classification and Grading System. Intl Ophthalmol 1986;9:207-225.

LENS Photo Grading Form

Subject ID#_____ Grader:_____ Date Graded:_____ Eye: R L

Red Reflex: Absent Present

Iris Pigmentation	Code
≤ Standard 1	1
≤ Standard 2	2
≤ Standard 3	3
> Standard 3	4
Can't Grade	8

Slit Lamp: Absent Present

Nuclear Color	Code
< Standard 2	1
< Standard 4	2
< Standard 7	3
≥ Standard 8	4
Can't Grade	8

Marcher (Neitz):

Anterior: Absent Present

Posterior: Absent Present

Nuclear Sclerosis:

Standard Photographs 1-6. Give decimal equivalent: (e.g. 1.0, 1.5, 2.0,…). If < Standard 1, mark 0.5; if > standard 6, mark 6.5.

_____.____

Pupil Diameter on Film:

Horizontal ____ ____ . ____

Vertical ____ ____ . ____

Opacity Present in reflex photo not seen in Marcher?

No	0
Questionable	1
Yes-other	2
Yes-PSC	3
Can't Grade	8

Cortical Fleck

None	0
Questionable	1
Present	2
Can't Grade	8

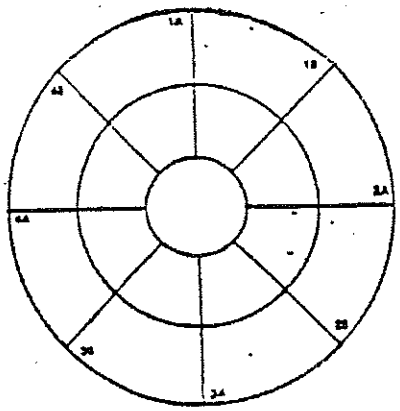
Lens Opacities Present: No Yes

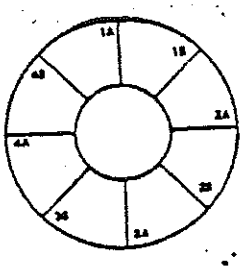
Cortical opacities (%): Absent Present

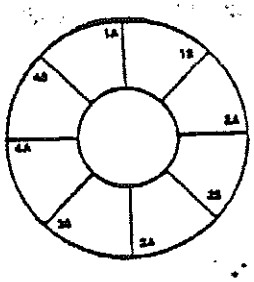
PSC (%): Absent Present

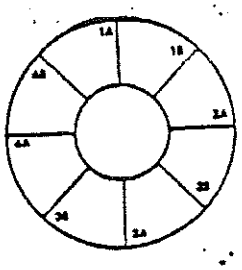
Vacuoles (#): Absent Present

WACOS: N Q Y CG









Mittendorf Dot: Absent Present **Pseudoexfoliation:** Absent Present **Other:** Absent Present

Exhibit 2. GRADING GRID