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Drusen Measurement from Fundus Photographs Using Computer Image Analysis

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Abstract: Drusen are yellowish deposits at the level of the retinal pigment epithelium and are frequently associated with age-related maculopathy (ARM). Drusen often change in size and number over time and may be followed by atrophic or exudative macular degeneration. A quantitative method to measure the development of drusen is needed for controlled studies of the natural history, prognosis, and treatment of ARM. An objective method is described using computer image analysis of fundus photographs for the detection and measurement of drusen. This technique enables us to measure both the area of drusen in the macula and the changes in the drusen pattern over time. Evaluation of repeated photographs showed reproducibility of 6.1%, whereas the reproducibility of processing photographic duplicates was 2.3%. Digitization with a high-quality linear array solid state camera did not change reproducibility significantly. [Key words: age-related maculopathy, computer image analysis, drusen, fundus photography, retinal pigment epithelium.] Ophthalmology 93:1575–1580, 1986

In the US, age-related maculopathy (ARM) is the leading cause of severe visual loss among the elderly.[1] ARM is almost always accompanied by drusen, although the role of drusen in the natural history of this disease is unknown. Most investigators believe that drusen are manifestations of retinal pigment epithelial disease; however, pathogenesis of drusen and even their constitution are not clearly understood.[2] Although drusen are compatible with good visual acuity, a large number of patients with drusen will have subretinal neovascularization and exudative disease or areas of retinal pigment epithelium atrophy, all of which have a devastating effect on visual function.[3–11]

Because most authors agree that the appearance of drusen precedes the development of ARM, any clinical study of the pathogenesis, clinical course, and efficacy of treatment must begin with the establishment of a reproducible method to evaluate the extent of drusen in the macula. In an effort to identify factors in the pattern of drusen that increase patient risk for development of ARM, a number of studies implemented semiquantitative techniques for evaluation of various drusen parameters.[12–16] Some studies have compared drusen photographs with standard photographs, grading the drusen in the test photograph as larger or smaller and more or less confluent or numerous.[12] In other studies, a finer grading of 1 to 4 or 1 to 3 was assigned to such parameters as size, number, distribution, and degree of confluence of drusen.[2] Although reports of the specific parameters of drusen found to be important in different studies have been inconsistent, most semiquantitative studies support the clinical impression that more severe drusen indicate increased risk of development of exudative maculopathy.

Because the area of the macula affected by drusen reflects the number of retinal pigment epithelial cells involved in ARM, a comparison of the surface area of drusen versus the area without drusen would permit consideration of a more relevant parameter. Human observers can count drusen that are not too numerous, can estimate drusen size, and can make some judgments about confluence. It is extremely difficult, however, to estimate an area prop-

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erly; we are more adept at estimating linear rather than areal fractions. Although drusen area was not measured in previous studies, it may be inferred that increased drusen size, number, and confluence usually represent an increase in the area covered by drusen.

In this study, we present an improved method for the quantitation of drusen from fundus photographs. Our method involves the use of computer image analysis techniques and allows us to measure the area of the macula covered by drusen as well as to obtain more accurate measurements of any parameters that were found to be important in other studies.

MATERIALS AND METHODS

PHOTO SELECTION

Color transparencies (Ektachrome EN, 100 ASA 300K [Eastman Kodak Co, Rochester, NY]) taken with a Zeiss FF3 fundus camera (Carl Zeiss, Inc, Thornwood, NY) and centered around the fovea were selected from the records of patients treated by the Retina Service of the Ophthalmology Department at New England Medical Center. A patient's fundus photographs were selected for this study if (1) drusen were visible in the macula, (2) repeated photographs were taken of the same eye at the same sitting (at least 3 photographs), and (3) photographs that had been taken of the same eye on multiple episodes over 2 or more years were available.

DIGITIZATION

The color slides were projected with the condensor photo enlarger through a green filter onto a linear array digitizing camera (Datacopy, Mountain View, CA). The green filter was selected to enhance the contrast of the yellow drusen against the red retinal background. Slides were digitized at a resolution of 512×512 picture elements (pixels) and at 256 gray levels (8 bits). From the digitized images, the central macular area (comprised of 256×256 pixels), was stored on a computer disk.

In order to compare photographs taken over time and to evaluate repeat photographs taken at the same time, digitized images from the photographs had to be registered and aligned. Manual alignment of the images was achieved by displaying a previously stored image on the red channel of the image display system (Adage, Inc, Billerica, MA). A new image to be aligned with it was continuously digitized and displayed on the green channel, thus enabling the operator to see both images at the same time; camera position was adjusted with a micro-manipulator to allow horizontal, vertical, and rotational movements. Small changes in magnification of the photographs were corrected by changing the distance of the camera from the slides.

IMAGE PROCESSING

A basic technique used to distinguish objects from background is called thresholding.[17] A threshold gray level is selected, and every picture element in the image that has a higher gray value than the threshold is set to 255 (white); all other picture elements are set to 0 (black). Assuming that drusen in the image are significantly brighter than the background, proper selection of one threshold should detect all drusen throughout the image. However, owing to illumination variations and to pigmentation changes across the macula, drusen in one area of the macula may actually be darker than the background at other points on the macula. It was necessary, therefore, to apply an adaptive thresholding procedure, which changed the threshold selection according to local properties in the image.

Our technique is a modification of the adaptive thresholding reported by Chow and Kaneko.[18,19] The image is divided into small, nonoverlapping windows of 8×8 pixels. It is assumed that if such an 8×8 window contains both a part of a drusen and a section of the background within it, then the gray level histogram of all 64 pixels in that window should be bimodal, ie., having two distinct lobes or peaks. One lobe contains the gray levels of the pixels included in the bright drusen, and the other lobe contains the pixel values obtained from the dark background. If the valley between the two lobes can be found, its level can serve as a proper threshold for this 8×8 area in the image. To simplify calculations, we based our estimation on whether a histogram was bimodal or unimodal on the standard deviation of the gray levels in a window. This was done with the assumption that a bimodal distribution is likely to have a larger standard deviation than a unimodal distribution. For all windows defined as bimodal by this criterion, the threshold value was calculated as the median of the gray levels within the window. This again was an approximation; we assumed that all bimodal windows contained about equal parts of drusen and background. When all bimodal windows were assigned a threshold value, the thresholds over the entire image were interpolated for all of the windows using two-dimensional linear interpolation. Based on those interpolated smoothed thresholds, a threshold value was calculated for each point within the windows, and each point was designated as either drusen or background.

MODIFICATIONS TO REDUCE FALSE ALARMS

There are two common causes of "false alarms," or identification of background points, as drusen. First, error may result from correct identification of windows containing blood vessels as having bimodal distribution but then designating the background retina next to the vessel as drusen. Second, drusen usually occupy only a small fraction of the retinal area, and thus many windows within the image are not assigned threshold values based on their gray level but rather on the propagated interpolation value from neighboring areas containing drusen. This may result in low threshold followed by identification of large sections of background as drusen.

The operator eliminated artifacts caused by vessels or pigmentation clumping in the image by using a bit pad graphics input to manually delete thresholds that were assigned to these areas. An erroneously identified threshold point was eliminated simply by positioning the cursor next to it on the display screen. This maneuver was ac-

complished quickly because the cursor needs to be only within a neighborhood of 8×8 pixels from the appropriate artifact point, resulting in a "vacuum cleaning" effect. The elimination of those artifactual thresholds does not have to be complete; it is sufficient to "clean" only areas with many such erroneous thresholds. If a few dispersed false thresholds remain, then the next part of the processing will eliminate their effect. This automatic correction was achieved by setting the threshold in an area not populated by drusen to the highest threshold level found in the image. This method assured a high threshold level set at areas of the image that did not have many drusen, and thus the effect of singular threshold points left after manual editing would be significantly reduced during the interpolation stage. The manual editing and the automatic correction were done before the interpolation of window thresholds.

DATA ANALYSIS

After the image was converted to a binary image, the number and percent of points selected as drusen could be calculated. Comparison of photos taken over time could be done easily with a multicolor display; the early image was displayed in yellow and the late image in the blue channel. Thus, area of the image where drusen appeared in later photos but were absent earlier were displayed in blue, and areas of the image where drusen disappeared were yellow. The drusen that did not change appeared as white. In addition to the visual display, the actual percentage of new drusen and the percentage of drusen that disappeared over time were calculated.

REPRODUCIBILITY

To test the reproducibility of our technique, we used repeat photographs taken of the same eye at the same sitting. Three repeat photographs from four different eyes were used, all with confluent drusen. The images were digitized, aligned, and processed as described above, and the number of points identified as drusen in each image were calculated. Reproducibility was defined as the coefficient of variation (standard deviation/mean).[20,21] These values were calculated for every set and reproducibility was averaged. The photographs selected for testing were of usual clinical quality, and the patients in most cases had some lens opacities, as expected in patients with macular disease.

Because photographic variables such as variation in illumination and composition of the fundus photograph affect measurement, photographic duplicates were used to evaluate the lowest boundary of the reproducibility possible with our technique. For that purpose, four slides from different eyes were sent to a commercial laboratory and two duplicates were obtained of each. Duplicates pairs were digitized, processed, and compared to each other.

RESULTS

Figure 1 illustrates the typical processing of an image. The original digitized image is displayed in the top right corner. Windows selected as having bimodal distribution of gray levels are marked by dark points on the top left image. The white points on the same image indicate windows that were assigned the maximum threshold value because they were not in the immediate neighborhood of a bimodally distributed window. The binary output image representing drusen in white and background in black is displayed in the bottom left corner. The image on the bottom right is the original image with the identified drusen marked.

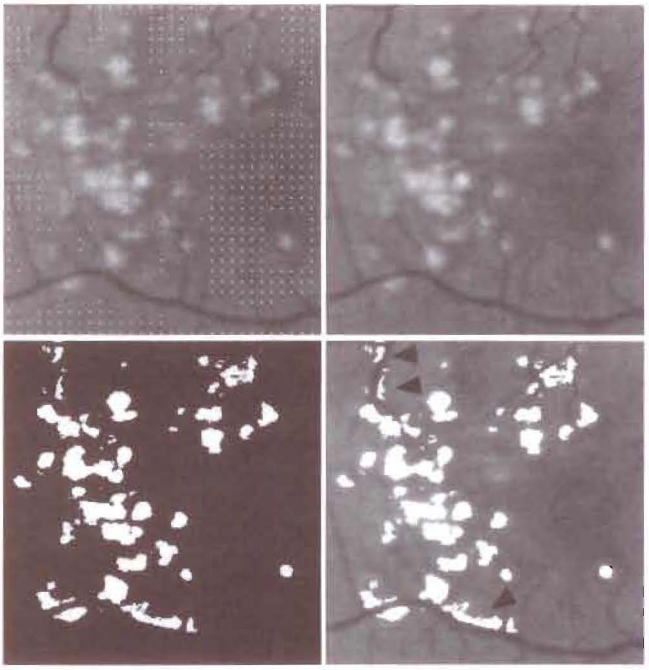

Fig 1. Drusen detection from fundus photographs without editing of vessel artifacts. *Top right*, the original digitized image; *top left*, the dark points indicate centers of windows that were identified as having bimodal distribution. White dots indicate windows that did not have neighboring windows with bimodal distribution and thus were set to the highest threshold value in the image. Notice dark points along the vessel at the bottom and the vessels at the top of the frame. *Bottom left*, the final processed image output indicating drusen as white and background as dark; *bottom right*, the detected drusen superimposed on the original image. Notice a number of false alarm identifications of drusen next to vessels (black arrows). Notice a faint drusen in the middle of the image that was missed. The area of drusen detected in this image covers 9.1% of the image.

The effects of manual editing of vessel artifacts are demonstrated in Figure 2, which depicts the same image as in Figure 1, but digitized with a better camera (Datacopy). The false alarms were completely eliminated by the manual editing, and some of the previously missed drusen were correctly identified, owing to the improved contrast in this image.

Figure 3 illustrates the same process on a photo with confluent drusen. This image was also digitized with the Datacopy camera. Very little editing of vessel artifacts was needed in this case. This image and others of similar quality were used for the evaluation of reproducibility.

The comparison of two photos taken of the same eye at different times is illustrated in Figure 4. Drusen iden-

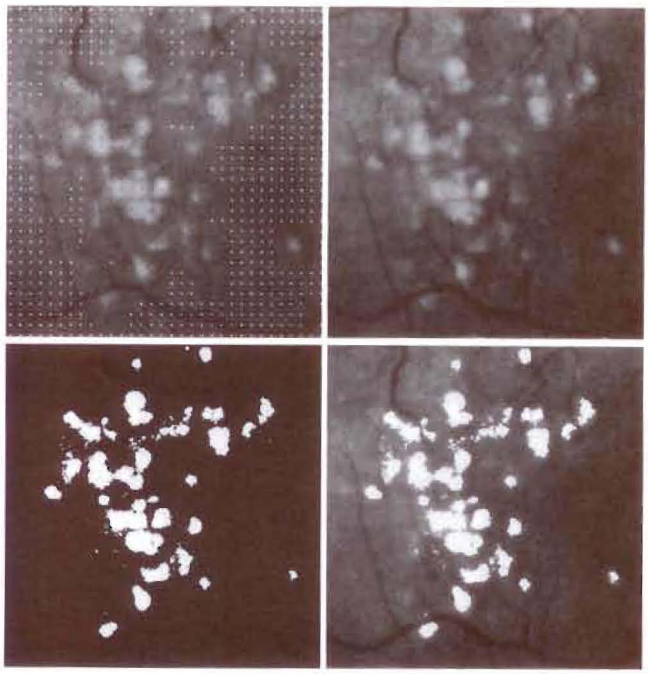

Fig 2. The same fundus photograph as in Figure 1, digitized with the higher quality Datacopy camera and processed with manual editing of drusen artifacts. *Top right*, the original digitized image; *top left*, the dark points representing areas that were identified as having bimodal distribution and were not edited by the operator. Notice that not all erroneous points on the vessel were eliminated by the operator. White dots in this image are more numerous because of the editing of the vessel artifacts. *Bottom left*, the binary output representing drusen in white and background in black; *bottom right*, notice that the drusen previously missed (Fig 1) have been identified here. The false alarms have been completely eliminated. The area occupied by drusen in this image is 7.1%.

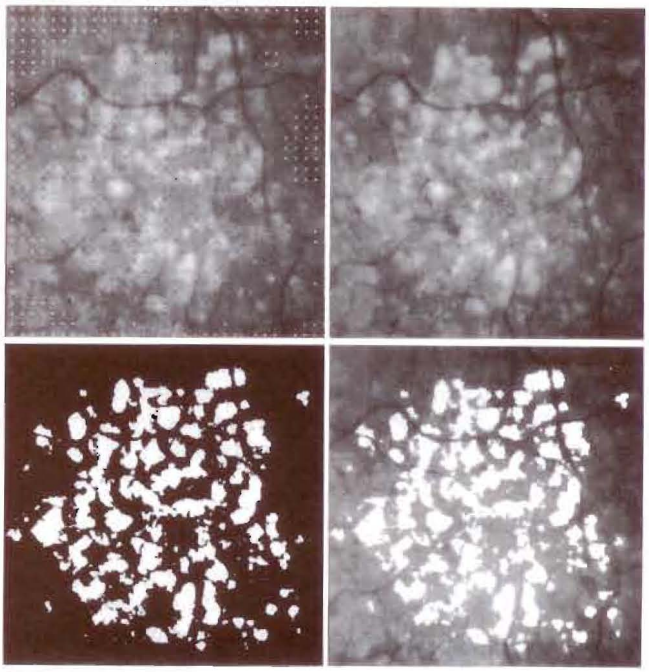

Fig 3. The same process as in Figure 2, but with a fundus image with a confluent, diffuse drusen pattern. Notice the general agreement between the identified drusen and human observation. The area of drusen measured in this image is 18.8%.

tified from the photo taken in 1980 are displayed in yellow and those from 1983, in blue. Drusen that did not change during that period appear as white, whereas drusen that disappeared between 1980 and 1983 appear yellow. New drusen (appearing after 1980) appear as blue points. Total drusen area was 6.4% in 1980 and 2.5% in 1983. Notice that residual atrophy of the retinal pigment epithelial is visible in areas where drusen disappeared (Fig 4B). Although these atrophic areas may be detected visually quite easily, they were not misclassified by the program as drusen. This was probably due to the relative small change in brightness associated with atrophic areas as compared to drusen. No manual editing of the images was required to prevent the detection of atrophic areas as drusen.

The reproducibility calculated from measurement of three repeat photographs on four eyes was found to be 6.1% (range, 4.2–10.4%). Processing of a photographic duplicate was used to estimate the lowest boundary of reproducibility. The reproducibility of four pairs of duplicates was found to be 2.3% (range, 1.3–3.3%).

The four pairs of photographic duplicates were processed in three different ways. The images were digitized twice with two different cameras: the high-quality Datacopy camera and a simple inexpensive Panasonic home video camera. Images were processed with and without manual editing of vessel artifacts. The results of the reproducibility calculation are reported in Table 1. Although the images obtained with the Datacopy camera are definitely better (sharper and with more contrast [compare Figs 1, 2]), the reproducibility was not significantly affected by the type of camera used. The accuracy of the result as evaluated by observation of the images clearly improved with editing of vessel artifacts. In addition to improved accuracy, manual editing of vessel artifacts improved reproducibility (Table 1). The variability in the measurements could be attributed in most cases to differences in area of drusen detected and only occasionally to completely missing some drusen in one image and detecting them in the other. In all cases, the variability was much more pronounced near the edges of the image than in the center. More variability was measured when the original photograph was decentered resulting in more of the vinggeting of the fundus camera affecting the drusen area on one side of the image.

DISCUSSION

The need to evaluate the role of drusen in the pathogenesis and prognosis of ARM has led a number of investigators to apply semiquantitative techniques to estimate the extent of drusen from fundus photographs.[12–16] Using trained observers, they have graded various parameters of drusen such as number, size, and confluence and have found a correlation between the severity of drusen and the risk of developing macular disease. Although the human eye is very capable in tasks such as detecting and

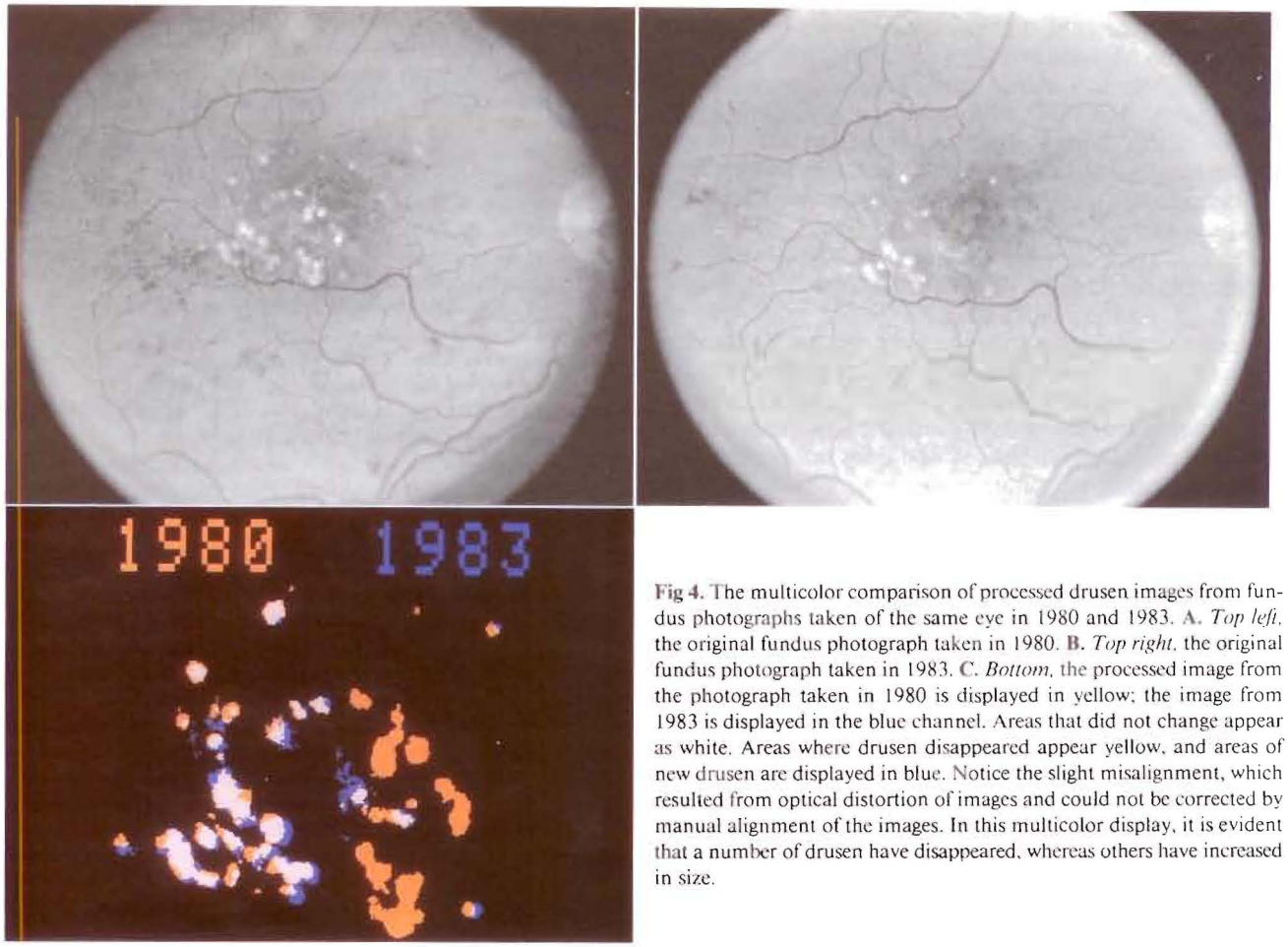

Fig 4. The multicolor comparison of processed drusen images from fundus photographs taken of the same eye in 1980 and 1983. **A.** *Top left,* the original fundus photograph taken in 1980. **B.** *Top right,* the original fundus photograph taken in 1983. **C.** *Bottom,* the processed image from the photograph taken in 1980 is displayed in yellow; the image from 1983 is displayed in the blue channel. Areas that did not change appear as white. Areas where drusen disappeared appear yellow, and areas of new drusen are displayed in blue. Notice the slight misalignment, which resulted from optical distortion of images and could not be corrected by manual alignment of the images. In this multicolor display, it is evident that a number of drusen have disappeared, whereas others have increased in size.

identifying drusen from fundus photographs, the human observer generally is unable to make accurate quantitative judgments from such observations. In most of these studies, therefore, only rough grading of three or four levels were used. The computer, on the other hand, can easily and accurately measure many parameters of the detected drusen. Computer image analysis of fundus photographs has been shown to be a highly reproducible and reliable method of quantitating parameters such as optic disc pallor, optic disc cupping, and identification of microaneurysms from fluorescein angiograms.[20,22,23]

During the arteriovenous phase of fluorescein angiography, drusen appear as sharply outlined areas of hyperfluorescence, indicating a retinal pigment epithelium window defect over the drusen, which allows choroidal fluorescence to be seen.[24] The size of the hyperfluorescent areas associated with drusen remains constant throughout fluorescein passage and persists after that passage. This indicates that the drusen body is permeable to dye and that there is leakage of dye through retinal pigment epithelium overlying the drusen. It is often noted that more drusen appear as hyperfluorescent areas during angiography than can be detected during ophthalmoscopy and that some hyperfluorescent areas do not retain fluorescein after dye passage.[24,25] This suggests that some retinal pigment epithelial window defects are not associated with drusen body. The existence of these nondrusen window defects precludes use of the higher contrast fluorescein angiograms for automatic or manual measurement of drusen.

It is known that drusen may appear, disappear, or become confluent, yet the prognostic significance of these phenomena remains unknown. The semiquantitative techniques previously used to evaluate the role of drusen

Table 1. Effects of Camera Type and Editing of Vessel Artifacts on the Reproducibility of Drusen Area Measurement from Photographic Duplicates

Duplicate Pair No.	Unedited* Panasonic Camera CV (%)	Edited Panasonic Camera CV (%)	Edited Datacopy Camera CV (%)
1	1.5	0.6	3.3
2	15.0	2.1	2.9
3	3.7	2.0	1.8
4	3.7	3.9	1.3

CV = coefficient of variation.
* Editing refers to manual editing of vessel artifacts.

in the pathogenesis of macular disease were not applied to evaluation of changes in drusen pattern over time. Although large drusen changes can be noted from a pair of photographs, it is difficult to obtain a quantitative descriptor of the change. By using image registration and multicolor display techniques, we are able to compare photographs taken over time and to evaluate the dynamics of drusen changes over time.

The technique we have presented here will enable researchers to obtain more reliable measurements of drusen from fundus photographs and will permit evaluation of new measurements that may be significant, such as drusen area and the dynamic change of drusen over time. Our technique is especially attractive because it can make use of the vast resources of data available as fundus photographs of patients with drusen and does not require any new photographic technique or instrumentation. With the advent of computer image processing systems, including those specifically designed for ophthalmology, this technique can be implemented in many research centers and can facilitate accurate and unified measurements of drusen from photographs.[26] Our comparison of scanning cameras has also shown that an expensive camera is not required to obtain good results. The reproducibility results obtained with the current technique are satisfactory and are comparable with the results of other image analyses of fundus photographs.[20]

In continuing studies, we expect to improve the sensitivity of detection to reduce the chance of misses even further and to implement an automatic method to eliminate the vessel and pigment artifacts, reducing the effect of operator judgment on the outcome. We also plan to develop an automatic registration and alignment program to shorten the time required for registration with manual alignment, which is the most lengthy part of image processing.[27] A better registration program will also give us the proper parameters to correct for distortions resulting from fundus photography and will increase the accuracy with which dynamic changes in drusen over time can be evaluated.

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