Measuring Geographic Atrophy in Advanced Age-Related Macular Degeneration

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PURPOSE. To present a method developed for measuring areas of geographic atrophy (GA) in advanced age-related macular degeneration.

METHODS. A microfilm reader projected the 30° fundus photograph of the macula. Retinal landmarks, atrophic areas, and spared areas within the atrophy were traced, without access to drawings of other years. The total atrophic area was calculated, as was the atrophy within a four-disc-area circle centered on the estimated foveal center. The configuration of the atrophy was documented.

RESULTS. Avoidable sources of discrepancy included variability in peripapillary atrophy seen on the photograph, and variability seen in the extent of the field. Reproducibility studies found a median absolute difference of 0.19 Macular Photocoagulation Study disc areas (DA) in total atrophy between repeat drawings, with 75% of repeat drawings having a difference of less than 0.33 DA. For central atrophy measures, there was a median difference of 0.08 DA, with 75% of pairs having a difference of less than 0.18 DA. Features making the definition of borders of GA difficult include the presence of drusen and pigmentary alteration, a fundus in which choroidal vessels are easily visible, and variation in the appearance of GA within a single area of atrophy.

CONCLUSIONS. This method provides a reliable means of measuring the size of atrophic areas in GA and will be useful for measuring longitudinal change. It may be difficult to determine whether central spared areas are present, and correlation with visual acuity and macular perimetry may be helpful. (Invest Ophtalmol Vis Sci. 1999;40:1761–1769)

Geographic atrophy (GA) is a form of advanced age-related macular degeneration (AMD) that is present in approximately 3.5% of the population 75 years of age or older.5,4 Unlike neovascular AMD (choroidal neovascularization, disciform scarring), the other form of advanced AMD, GA progresses slowly, over years, and spares the foveal center until late in the course of the disease.3–6 The primary visual impairment in GA arises from the presence of absolute scotomas (blind spots) corresponding to the GA,7,8 first in the parafoveal region and later coalescing and enlarging to involve the foveal center. When the foveal center is involved, there is severe central visual loss. This was seen in 42% of eyes with GA in a recent population-based study.9 When the fovea is not yet fully involved, the parafoveal scotomas impair visual performance by limiting the size of the seeing central region so that only a portion of a word or a facial feature can fit in the seeing area.6

In addition, recent work has shown that after the foveal center is involved, the size of the atrophic area is a critical determinant of reading rate, suggesting that the overall size of the atrophy may play a role in a patient’s daily activities.10

To study the progression of GA, it is critical to have a reproducible method for measuring the area of GA, both in its total extent and in involvement of the central region. This article reports the methods that have been developed to measure GA and the difficulties and sources of error that must be taken into account, in the context of a prospective natural-history study of GA with annual follow-up.

METHODS

Subjects

The subjects were participants in a prospective natural-history study of GA. Entry criteria were age 55 or older, with GA from AMD in at least one eye. Geographic atrophy was defined as one or more discrete areas, measuring 500 μm or more, of loss of retinal pigment epithelium (RPE), with a color and thickness change relative to the surrounding retina, and more prominent visualization of the choroidal vessels. A fluorescein angiogram was performed at baseline to exclude eyes with any evidence of choroidal neovascularization. Eyes with concurrent retinal disorders were excluded. The study adhered to the tenets of the Declaration of Helsinki. It was approved by the institutional review board, and written, informed consent was obtained from all patients.

Annual Examination

Stereoscopic pairs of color fundus photographs were taken at each annual visit. These included 30° stereoscopic photo-
Fundus Drawing

The fundus drawings (Fig. 1) and measurement of GA were performed in the Wilmer Photograph Reading Center. The method of drawing the fundus features and the GA followed the general methods used for drawing choroidal neovascularization in the Macular Photocoagulation Study, except that color fundus photographs were used rather than fluorescein angiograms. The grader chose the best 30° fundus photograph centered on the macula and projected it onto a sheet of white paper taped to the viewing surface of a microfilm reader (Aus Jena Dokumator DL-2; Handsel Scientific, Freehold, NJ). This system provides a $3 \times 3$ magnification of the slide, or $22.5 \times$ magnification of the fundus, in that the slide is approximately $0.12$ DA. Visual acuity was 20/264.

Before photography, the participants underwent a protocol refraction using an ETDRS chart to determine best-corrected visual acuity. They underwent a battery of visual function tests described elsewhere, including scanning laser ophthalmoscope (SLO) macular perimetry to determine the site of fixation and the presence of scotomas in the central field. A clinical examination was performed.

The coordinator for the GA study selected from 20 to 30 sets of photographs for the grader weekly. Approximately 8 hours of work per week were required to make the drawings from each batch of photographs, including drawing and adjudication. The borders of the areas of GA were drawn on one of the copies of the fundus drawing. The drawing was performed from a 30° fundus photograph centered on the macula, with

![Figure 1](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933583/)
the disc photograph used if the peripapillary atrophy was not adequately visualized in the macula photograph. Areas of GA were outlined in blue, and sites within the area of GA that were judged not to have undergone GA (called spared areas here) were outlined in a different color (Fig. 1B). Stereoscopic viewing of the 30° and 60° color photographs was used to determine the borders of the GA.

Completed drawings were reviewed with the first author (JSS) on a weekly basis. The fundus photograph was projected onto the grader’s drawing, and the drawing was reviewed critically. Any differences of opinion regarding the location of the boundaries of the atrophy were adjudicated between the grader and the first author. After this review process was completed, the drawing and photographs were removed from the Reading Center and returned to the study coordinator. No copy of the drawing of the atrophy was kept by the grader, so that each drawing was made independently of any drawings previously made.

The areas of atrophy were then measured from each drawing. A Summagraphics digitizing tablet (Summagraphics Corp., Fairfield, CT), connected to a microcomputer was used for this purpose. The operator traced the outline of the areas of atrophy and of the spared areas. A computer program (Paul Montague, University of Iowa, Ames) calculated the area in square millimeters on the drawing itself, using a polygonal estimation of area. This measurement was then converted to Macular Photocoagulation Study standard disc areas (DA; equivalent to 2.54 mm² on the retina).

Initially, each area was digitized three times, but after reproducibility studies (see below) showed excellent reproducibility, each area was digitized twice if there was good agreement between the first two measurements (less than 0.05 DA difference, or less than 0.5% of the total area); otherwise, additional measurements were made. Each area of atrophy in a given drawing was measured separately. Peripapillary atrophy was measured as well. Areas representing residual RPE within the area of GA were also measured. The measured areas were entered into a computer database for storage and further analysis, and data entry was checked for errors. The total area of atrophy was calculated by the computer as the sum of the areas of atrophy less the spared areas.

Central Atrophy Measure

The determination of the loss of seeing foveal retina is both the most difficult and one of the most critical aspects of measuring progression of GA. For the present study, the estimate of the foveal center was used as has been described. Even when there are no foveal localization problems, very small changes in area (such as the loss of a small spared central area) may have a profound impact on acuity and on visual function, but these are not captured well merely by giving the numerical amount of change in atrophic area. Scrupulous attention was given to detecting small central spared areas when making the fundus drawings. Although the grader and the first author were aware of the likelihood of spared areas within the atrophy, it was often difficult to be certain whether sparing was present. The central area was studied to determine whether there were areas preserved that did not show loss of RPE and retinal thickness. The presence of pigment or of xanthophyll served as clues for detecting preservation of central areas.

The amount of atrophy within a 4-DA circle (3000-µm diameter) centered on the fovea was used as the central atrophy measure; a 4-DA circle corresponds to the size of the central visual field we were testing using the SLO⁶⁻⁸ and to the middle circle in the recent international AMD grading system¹³ and is large enough to lessen the effects of small errors in foveal localization. This measurement is referred to as the central atrophy measure (Fig. 1a).

Configuration of Atrophy

Based on the fundus drawings, the configuration of atrophy was classified into one of six categories. Small referred to a single area of GA of less than 1 DA. Multifocal referred to two or more areas of GA of approximately the same size (Fig. 2A). Horseshoe referred to a horseshoe-shaped area of GA that often spared the center (Fig. 2B). Ring referred to a solid area of GA with sparing of the foveal center. (Fig. 2C). Noncentral sparing was a solid area of GA with sparing of areas other than the center (Fig. 1A). Solid was a single area of GA larger than 1 DA without sparing. (Additional small satellite areas of GA were seen in some eyes with horseshoe, ring, and solid configurations.) In some eyes, several categories could be present; for example, there may have been a horseshoe with other multifocal areas. In these cases, the drawing was classified by the predominant configuration.

Avoidable Sources of Variability

Preliminary evaluation of repeat drawings early in the study identified two sources of error that could be eliminated to improve the reproducibility and the accuracy of measurement of change in the size of the atrophic area from year to year. The first source of error was related to peripapillary atrophy. Errors included neglecting to draw peripapillary atrophy and having different extents of the disc visible on the fundus photographs taken at different annual examinations. The error associated with different extents of the disc visible on the photograph was resolved by ensuring that the same cutoff line demarcating the peripapillary atrophy was used for all drawings of a given eye (Fig. 1B). The fundus drawings were also reviewed longitudinally, and a common cutoff for the peripapillary region for each eye was defined, based on the photograph showing the least nasal extent of peripapillary atrophy. The extent of the disc visible remained nonuniform across all the eyes in the study; however, this procedure made it uniform for a given eye from year to year. Other possible ways of overcoming error introduced by peripapillary atrophy include either measuring only total atrophy without noncontiguous peripapillary GA or measuring total atrophy only within a certain region, such as a 6000-µm-diameter (16-DA) circle. Because noncontiguous peripapillary atrophy may evolve into atrophy continuous with macular atrophy, an overestimate of rate of enlargement would be obtained by not including noncontiguous peripapillary GA. It was important in this study to measure the total area of atrophy, because we wanted to determine whether large areas of GA continued to enlarge.

The second source of error was in eyes in which the atrophy extended to or beyond the edge of the photograph. A uniform cutoff of these areas for the different drawings of a given eye was used for the purpose of measurement and after enlargement from year to year. The cutoff line was chosen based on the photograph showing the least peripheral extent of the field.
Delineation of Atrophy

For many eyes, the GA was easy to delineate, based on a color change between the GA area and the surrounding retina (Fig. 1) and the prominent appearance of choroidal vessels through the atrophy. However, GA delineation is not always that clear cut. In a lightly pigmented fundus, the color differentiation may not be as clear and the choroidal vessels may be visible through the uninvolved retina as well (Fig. 3A). In some patients, the choroidal vessels seen through the atrophy appear yellow rather than red, and sometimes the choroidal vessels may have two different appearances within the same area of atrophy, making the identification of the total area of atrophy difficult (Figs. 3B, 3C). The area of GA may border on an area of numerous drusen or RPE hypopigmentation, which may complicate the delineation of the border of atrophy. In some patients, there may be overlying calcification, and small areas of GA may be difficult to distinguish from large or confluent drusen (Fig. 3D). The variation in the appearance of GA makes it hard to use a standard photograph.

Other clues can often be helpful for the delineation of GA in difficult cases. Stereoscopic viewing of the fundus photographs often delineates the area of GA as an area of depression and decreased retinal thickness. Sixty-degree photographs are often useful for determining the border of GA, and that determination can then be applied to the 30° photograph. Areas of GA are sometimes outlined by a border of hyperpigmentation.

In performing any detection task such as determining the borders of GA, it is important to try to keep the same criterion for the presence of GA. For example, if a grader at one time drew only areas she identified as definite GA and at another time included any areas she identified as questionable GA, the amount of atrophy drawn would be different and would be difficult to compare from one drawing to the next. A strict criterion for GA was used for this study. Only definite GA was included in the drawing of atrophic areas. Those areas that possibly, but not definitely, had GA, were indicated by symbols on the drawing (Fig. 4), so that we may refer back to them for longitudinal comparisons in the future, but questionable areas were not measured as GA.

Peripapillary Atrophy

Peripapillary atrophy was drawn only when it was judged that definite GA was present bordering the disc, rather than other peripapillary pigmentary alterations commonly observed. Figure 5 represents the minimum degree of atrophy that would be included as peripapillary atrophy.

SLO Macular Perimetry

SLO macular perimetry was performed on all patients in this study at each annual examination. This technique allowed the observation and documentation of the stimulus and its location directly on the retina in real time, so that fixation and scotomas...
could be accurately mapped on the retina. The technique is fully described elsewhere.\textsuperscript{8} For the purposes of this study, the SLO results were compared with the fundus drawings to determine whether functional spared areas in the SLO analysis were detected on the fundus drawings. The drawings were done independent of SLO findings.

RESULTS

Reproducibility of Fundus Drawing and Area Measurement

To date, 865 drawings of 236 eyes with GA from 148 patients have been completed, and areas of total and central atrophy have been measured. Included in these are 43 repeat drawings of different eyes at different visits, to determine reproducibility. Approximately 15% of the first 100 drawings were repeated and showed good reproducibility, and sporadic repeat drawings of visits were performed thereafter. The reproducibility of the fundus drawing and measurement process was explored for each phase.

Variability in Drawing the Areas of Atrophy

One grader (YT) made all drawings from the fundus photographs, as has been described, and all photographs and drawings were reviewed and adjudicated with the first author (JSS). The adjudication process was found to be important for defining borders of atrophy and identifying spared regions. The grader was given 43 sets of photographs of 43 eyes to draw twice. (Each set consisted of all fundus photographs from a single visit for the eye to be drawn, to be called visits in this study.) She and the first author were unaware that these were repeat drawings, because none of the drawings was kept by the grader, and the repeat drawings were made at different sessions and incorporated into a set of visits to be drawn for the first time. The repeat drawings were digitized separately from the original drawings.

Table 1 presents the differences between repeated drawings. Thirty of the 43 pairs (70%) showed no difference in the number of atrophic areas, number of spared areas, or configuration of atrophy and had less than a 0.5-DA difference in total atrophic area. Of the 13 pairs with differences in one or more measures, 9 had differences in more than one measure and 4...
had differences only in area. Three pairs had a difference between 0.5 DA and 1 DA, and three pairs had a difference of more than 1 DA (Fig. 4). There was a difference in the number of atrophic areas identified in three pairs, in each of which a small peripheral area was included in one drawing and not in another. There was a difference in the number of spared areas in seven pairs of drawings. The configuration of atrophy was different in six pairs. In three pairs, one drawing was judged as showing solid GA without sparing and the other showed central sparing. Two pairs were judged to have a multifocal con-

**Figure 4.** Discrepancy between drawings. (A) This is one of the four fundus photographs for which there was a difference of greater than 1 DA on repeat drawings. (B) One drawing treated the superior area as questionable GA and did not include it in the areas of GA to be measured. Total atrophic area was 1.1 DA. (C) The other drawing included the superior area as GA. Total atrophic area was 2.8 DA. (D, E). At 3.5 years, there was a horseshoe of atrophy present including the superior region. It was still difficult to delineate the GA from the surrounding retina.
configuration in one drawing and a horseshoe or solid configuration in the second, and one pair showed central sparing in one drawing and sparing in a noncentral area in the other.

The actual measurement of area showed little difference between the two drawings of the same eye at the same visit. The median difference in total atrophic area for the 43 pairs of drawings was 0.17 DA. Seventy-five percent of pairs had a difference in total atrophic area between drawings of less than 0.33 DA, and 90% of pairs had a difference of less than 0.72 DA. Three pairs (7%) had differences greater than 1 DA (Fig. 4). As a percentage of the total atrophic area, the median difference between drawings within a pair was 4.6%, with 75% of pairs having a difference of 9% or less, and 90% of pairs having a difference of 15% or less (Fig. 6).

Central Atrophy Measure

Variability in Localization of the Foveal Center. Variability in the localization of the foveal center leads to variability in the central atrophy measure. To obtain an estimate of the reproducibility of the localization of the foveal center, for every 10th patient (32 eyes, 14% of all eyes in the study) the localization procedure for the foveal center described in the Methods section was performed twice, and the distance between the two determinations of the foveal center for each eye was measured. The median distance between these foveal center determinations was 178 µm, with a range of 0 to 600 µm. Twenty-five percent of the eyes had distances between foveal-center determinations of 400 µm or greater. Given this degree of variability, it was believed that a measure of the atrophy immediately surrounding the foveal center was bound to be inaccurate, which is why a larger circle of atrophy centered on the fovea was used as the measure of central atrophy.

Variability in the Central Atrophy Measure. Of the 236 eyes whose photographs have been drawn, for 60 (25%) it was necessary to rely primarily on the estimation procedure for the localization of the foveal center described in Methods, because there was little vascular detail and no xanthophyll was visible. To determine the effect of variability in foveal localization on the central atrophy measure, a study was undertaken to compare the central atrophy measure using two foveal local-

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**Table 1. Differences between Pairs of Repeated Drawings**

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Total pairs: 43; total pairs without any differences: 30 (70%); total pairs with differences in one or more categories: 13 (30%); pairs with differences in each category: area, 6; number of atrophic areas, 3; number of spared areas, 7; configuration, 6. Nine pairs have discrepancy in more than one category.

* Difference between pairs of drawings of 0.5 or more Macular Photocoagulation Study disc areas. For all categories, 0 indicates no difference, and Y indicates a difference.
ization methods. For 35 eyes for which there was clear evidence of the location of the foveal center on the fundus photograph (using xanthophyll or vascular pattern), a comparison was made between the amount of central atrophy measured using this clinically defined foveal center and the amount of central atrophy measured using the estimation method (distance from the disc). There was a median absolute difference of 0.08 DA between measurements based on the two different foveal localizations, with a range of 0 to 0.7 DA. Seventy-five percent of the drawings had a difference of less than 0.18 DA, and 90% had differences less than 0.34 DA.

For the independent pairs of drawings used for assessing reproducibility of the total atrophy measure, the central atrophy was measured and compared, using a single determination of the foveal center (the foveal location that was present on the landmark drawings on which the areas of atrophy were traced). The median difference in central atrophy for the pairs was 0.06 DA; 75% of pairs had differences of 0.16 DA or less, and 90% of pairs had differences of 0.26 DA or less.

**Variability in Digitizing the Drawings**

For the first 100 fundus drawings, one grader traced all the areas on each drawing three times on the digitizing tablet. The average SD of the area measurement for the 147 areas of atrophy traced was 0.004 DA, with a maximum SD of 0.03 DA. The mean area was 3.45 DA, with a range of 0.02 to 14.4 DA. There was an increase in the SD with an increase in the size of the area measured ($r = 0.68$), with a mean coefficient of variation of 0.25%. Similar results were obtained for digitization of the peripapillary atrophy and the areas of spared retina within the atrophy. Thus, there was very little error in the digitizing process by a single observer. The central atrophy measurements were similarly highly reproducible, with an average SD of 0.01 DA.

To assess interobserver variability in digitization, 10 drawings were randomly chosen and were given to two employees to digitize. Thirty areas were traced and measured from these drawings. The median absolute difference between the measurements was 0.005 DA. The largest difference was 0.10 DA in an eye with a large area of atrophy; all other areas had differences of 0.03 DA or less.

**Comparison of SLO Findings with Fundus Drawings**

For a separate study, the SLO site of fixation was determined for a group of eyes with bilateral GA. Of 34 eyes with GA in the present study that were classified as solid without central sparing on the basis of the fundus drawings, 5 (15%) were found to have spared central areas that were used for fixing a cross in the SLO. Two of these eyes had ETDRS chart acuities between 20/40 and 20/70; one had an acuity of 20/107, and two had acuities worse than 20/200; these latter eyes could not use the spared area effectively for letter or word reading.

Clues to spared areas are the presence of normal (or sometimes exaggerated) RPE pigmentation and areas of hyperpigmentation. However, hyperpigmented areas may still be atrophic, and a distinction must therefore be made between areas in which it is judged that remaining retinal tissue is present and areas that appear atrophic but have increased overlying pigmentation. Similarly, there may be residual xanthophyll in some eyes that have atrophy involving the fovea.

Nine eyes with GA considered on the basis of the fundus drawing to have solid atrophy without central sparing had visible xanthophyll. Four of these nine eyes (44%) actually had some central sparing on the basis of the SLO testing. Two of these eyes had good chart acuity (20/55 and 20/55), whereas the two other eyes had acuities below 20/200, and the spared areas could not be used for reading.

**DISCUSSION**

Our reproducibility studies show that the method of measuring the areas of GA discussed here was a reliable one and provided reliable measurements of total atrophy longitudinally over time for patients with GA. The foveal center determination provided an adequate basis for measuring the atrophy within the central 4 DA of retina at present but could not adequately capture the involvement immediately surrounding the foveal center because of variability in the determination of the foveal center. The identification of an area as spared on the basis of the fundus photograph alone remained difficult in some cases.

There is evidence that even in patients who have lost foveal vision, the area of atrophy is strongly inversely correlated with the maximum reading rate. Thus, the ability to slow down the spread of atrophy even in later stages of GA may have a positive impact on visual function in everyday situations. For this reason, the total area of GA was measured rather than the area enclosed within a large circle (16 DA for example) centered on the fovea. Future testing of potential interventions in eyes with large areas of GA may provide evidence of a beneficial effect, because we now know that even these eyes continue to have progression of GA.

There is more variability in determining the number of atrophic or spared areas than there is in the actual measurement of atrophic area. At times it is difficult to determine whether one area of atrophy is connected to another. Although describing the configuration of GA is useful, it is not as reliable as atrophic area. Prospective studies should therefore rely on area measurements, rather than on configuration changes or changes in the number of atrophic areas.

The measure of central atrophy is not an adequate description of the changes occurring in the foveal center, because location of the atrophy, more than area, is the critical determinant of central visual acuity. Tiny changes in spared retinal area that would be insignificant in the periphery can critically impact foveal vision, and these small changes are not captured well by measuring the atrophic area alone. Finally, because of changes in the pigmentary character of the fovea before development of GA and because of the difficulty in determining whether a tiny retinal area is truly spared, it is difficult to be as certain of the foveal delineation of atrophy as it is to ascertain the more peripheral delineation. These difficulties are complicated by the difficulty in defining the location of the fovea itself, because often landmarks are not apparent. Spared areas may be difficult to detect, and correlation with acuity or with such techniques as SLO macular perimetry may be needed to determine whether a patient can use an area that is pigmented or appears to have preserved RPE.

This study examined only reproducibility by one team of graders and did not determine variability among multiple graders. It shows that strict criteria can be adopted and maintained that provide reproducible results within one grader team. Fur-
ther work is necessary to determine how to transmit the criterion level to other graders, because standard photographs would have to vary with surrounding fundus color, the presence of drusen, and other factors (Fig. 3), and stereoscopic views are also important.

At the start of the study, we decided to adopt the drawing of the fundus features and atrophy using a microfilm reader (Dokumator; Handsel Scientific), as was used for study of choroidal neovascularization in the Macular Photocoagulation Study. The baseline drawing of retinal vessels and landmarks was used for drawing the atrophy in all subsequent years. Although the same fundus camera was generally used in subsequent years, there remains the variability in the fundus image caused by differences in alignment in the various years. Future studies may use image registration techniques to avoid this problem.

Fluorescein angiography was not used for measuring areas of GA; because of costs and the minor invasiveness of dye injection, only baseline fluorescein angiograms were performed on all patients. At subsequent visits, fluorescein angiography was performed only when there was a suspicion that choroidal neovascularization was present. A comparison of fluorescein angiography and color fundus photography in our laboratory suggests that similar delineations and areas would be obtained with both techniques.

Further validation of this technique of measuring GA area will come from applying it to the sequential reading of photographs from subjects who are observed over time. Similarly, a systematic approach to correlation with functional changes will be helpful in assessing the significance of changes in GA area.

This technique of measuring the atrophic area was reproducible and suitable to measure longitudinal changes in area. The techniques and ways to ensure reliable data can be readily adapted to future computer image processing capabilities. However, it is a labor-intensive approach. It was necessary to use this approach for the natural-history study because it was desired to document whether there was growth of all areas of atrophy or only of smaller initial areas. For future studies, the goal would help to determine the methodology used. The fundus photograph might be divided into portions of 3000- and 6000-μm circles, and the involvement of these portions with GA could then be assessed. For treatment trials, entrance criteria could be defined that would make quantification of change in area simpler (for example, GA of size less than 5 DA, with all borders discrete and well seen on a 30° photograph). Currently, image analysis for GA is daunting, but in the future with choice of appropriate wavelengths and better imaging techniques it may be possible to automate more of the procedure and the registration process from year to year. Given the slow rate of enlargement, evaluation at not less than annual intervals would be recommended.

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References