

# 3 Moorfields Regression Analysis

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## INTRODUCTION

It is well established that structural changes at the optic nerve head (ONH) are an early and prominent feature of the glaucomatous disease process, so it is to be expected that measurements of ONH structure should be able to distinguish between glaucomatous and healthy nerves. The HRT II derives a large number of measurement parameters, both for the ONH as a whole (“global”) and for more localized ONH regions (“predefined segments”) (see Chapter 2). Different mathematical approaches have been applied to the problem of deriving a suitable algorithm that can make best use of all the measurement data to distinguish between normal and glaucomatous eyes. The most frequent approach is to take a group of healthy nonglaucomatous eyes and a group of glaucomatous eyes and submit all the measurements generated by the HRT to a linear discriminant analysis.<sup>1,2</sup> The output of such an analysis is a linear combination of the parameters that best distinguish between the two groups. This approach makes no assumptions about the parameters that are most likely to be useful, but the algorithm derived by the analysis is sensitive to the composition of the two subject groups taken as representative of “normal” and “glaucomatous.”

An alternative approach is that taken with Moorfields Regression Analysis (MRA). The form of the analysis was derived from a prior knowledge of physiological relationships, i.e., the dependence of neuroretinal rim area on optic disc size,<sup>3,4</sup> the possibility that neuroretinal rim area may decline with age,<sup>5,6</sup> and knowledge of the glaucomatous process (e.g., narrowing of the neuroretinal rim).<sup>7,8</sup> Although narrowing of the rim is said to occur preferentially in some regions of the ONH, it may occur in any region. For this reason, the algorithm was based on an analysis of all segments of the ONH. The approach was first applied to planimetry (measurements from ONH photographs)<sup>9</sup> and then to HRT images.<sup>10</sup>

The algorithm used in the MRA is derived from measurement data taken from a group of 112 normal eyes. Any ONH that is determined to be “outside normal limits” is not necessarily glaucomatous but is statistically outside the normal ranges for the group of eyes in the normative database. The decision as to whether “outside normal limits” represents “glaucoma” is a clinical judgment made by considering all clinical information together.

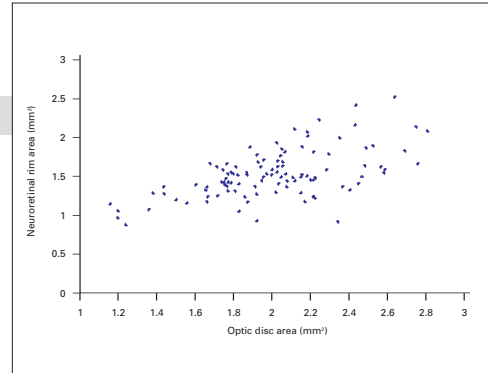
## SETTING NORMAL LIMITS

It is well established that neuroretinal rim area is related physiologically to ONH size.<sup>3,4</sup> This relationship is illustrated in Figure 3.1 for the eyes in the HRT II database. There is a tendency for the variability in neuroretinal rim area measurements to increase as the measurements themselves increase.

A logarithmic transformation is made to normalize the variability distribution. MRA makes use of the relationship between log neuroretinal rim area and optic disc area to define the normal ranges. Figure 3.2 illustrates the linear regression line between log neuroretinal rim area and optic disc area (marked “50%”). This is the “average” or “predicted” relationship between log neuroretinal rim area and optic disc area. The lower three lines represent the lower 95.0%, 99.0%, and 99.9% prediction intervals for the same relationship. Thus, for the 95.0% prediction interval, 95.0% of normal eyes would be expected to have a neuroretinal rim area above that interval line. The same reasoning applies to the 99.0% and 99.9% prediction intervals. These intervals are calculated for the ONH as a whole and for each of the six predefined sectors.

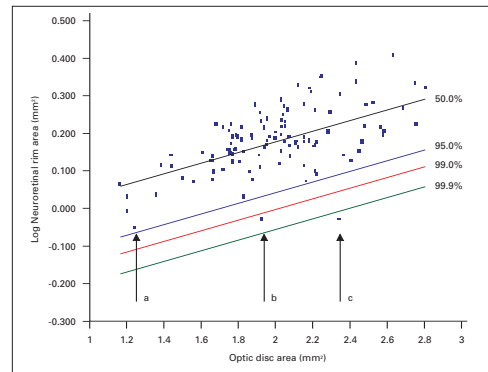
The classification for each ONH segment is displayed on the reflectivity image. A red *X* denotes “outside normal limits,” a yellow exclamation mark denotes “borderline,” and a green check denotes “within normal limits” (Figure 3.3).

The prediction intervals for neuroretinal rim area should be regarded in the same way as the probability symbols for abnormality in the reports from automated perimeters. The closer the top of the green bar gets to the lower prediction intervals, the greater the probability that the rim area is abnormal. The MRA Report given in the HRT II software enables a visual inspection of where the neuroretinal rim area lies in relation to the normal ranges (Figure 3.4).



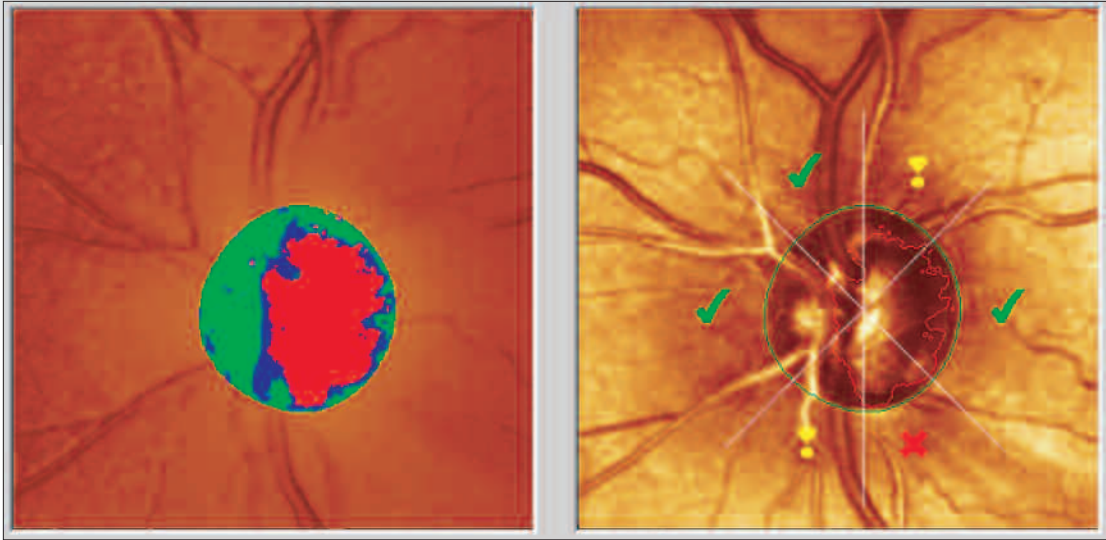
**Figure 3.1**

The physiological relationship between neuroretinal rim area and optic disc size in the eyes in the MRA normative database.



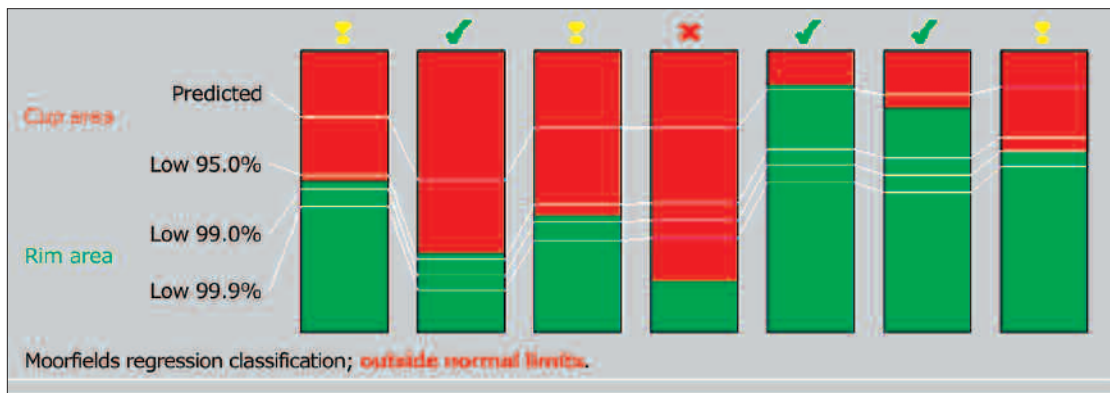
**Figure 3.2**

Plot of log neuroretinal rim area against optic disc area for the eyes in the MRA normative database, displaying the linear regression line and the lower 95.0%, 99.0%, and 99.9% prediction intervals. Three eyes with similar neuroretinal rim area are marked (a, b, and c). The neuroretinal rim area for “a” falls within the normal range because the optic disc is small. That for “b” falls between the 99.0% and 99.9% prediction intervals because the optic disc is of normal size. That for “c” falls below the 99.9% prediction interval because the optic disc is large. These are the lines marked on the Moorfields Regression Analysis Report given in the HRT II software, shown in Figure 3.3.



**Figure 3.3**

An example of a glaucomatous eye in which the neuroretinal rim area in some optic disc segments lies "within normal limits" (green check), some are "borderline" (yellow exclamation mark), and one is "outside normal limits" (red X).



**Figure 3.4**

MRA: The neuroretinal rim area (in green) and optic cup area (in red) are displayed as a series of bars for the whole disc (leftmost) and each predefined segment (left to right: temporal, supero-temporal, infero-temporal, nasal, supero-nasal, and infero-nasal). The narrower the neuroretinal rim, the shorter the green bar and the nearer the top of the bar gets to the lower prediction intervals. If the top of the green bar lies above the 95.0% prediction interval, then the disc or disc segment is classified as "within normal limits." If the top of the green bar lies between the 95.0% and 99.9% prediction intervals, then the disc or disc segment is classified as "borderline." And if the top of the green bar lies below the 99.9% prediction interval, then the disc or disc segment is classified as "outside normal limits." The most abnormal of the seven classifications (whole disc and six predefined segments) gives the overall classification for the optic disc.

In the subjects in the normal database, the neuroretinal rim area was also found to be dependent on subject age for the global measurement and in the temporal and supero-temporal measurements. Figure 3.5 illustrates this relationship for the global neuroretinal rim area. Subject age is taken into account when calculating the prediction intervals for global, temporal, and supero-temporal neuroretinal rim area in the HRT II software.

## INTERPRETING MOORFIELDS REGRESSION ANALYSIS

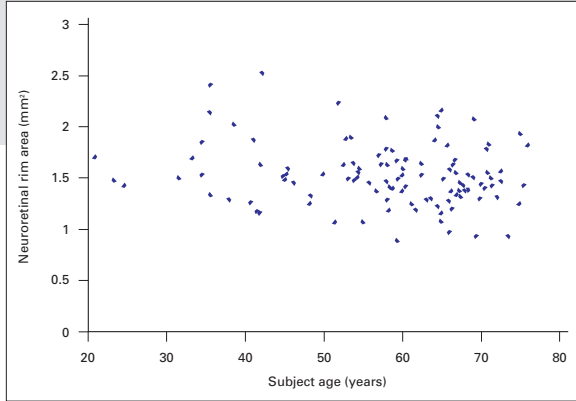
No commercially available imaging device is able to discriminate perfectly between normal and glaucomatous eyes—there is an overlap in measurements between the two. This is illustrated in Figure 3.6. At certain levels of neuroretinal rim area there is, therefore, uncertainty as to whether the measurement is within or outside normal limits. In MRA, this zone of uncertainty has been designated “borderline.”

MRA has been applied to a large number of normal and glaucomatous eyes from four different research centers.<sup>11</sup> HRT II classification of normal and glaucomatous eyes is given in Table 3.1. Similar results have been reported in a more recent publication.<sup>12</sup>

Table 3.1 gives proportions of normal and glaucomatous eyes classified into each HRT II classification group. However, the actual numbers of normal and glaucomatous subjects in each classification group depend on the prevalence of glaucoma in the population undergoing examination. Figure 3.7 illustrates the case of a 2.4% glaucoma prevalence.<sup>13</sup>

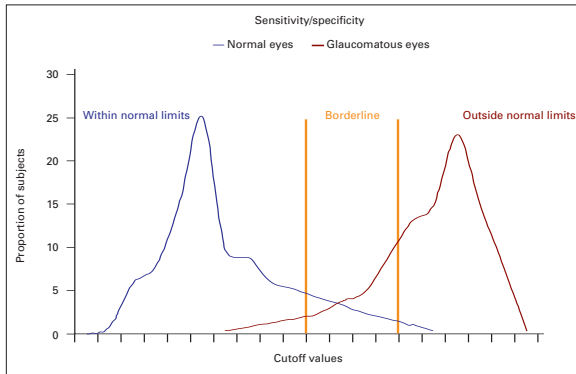
Table 3.2 gives the proportions of eyes, by true diagnosis, in each HRT classification group for a population with a 2.4% glaucoma prevalence. Note that only 4% of borderline cases will have glaucoma. Also note that because of the much larger number of normal subjects in the general population, even a low misclassification rate of 7% results (as it would with other imaging devices) in more normal subjects being misclassified as “outside normal limits” than glaucomatous subjects being correctly classified as “outside normal limits.”

Whereas a 2.4% prevalence might represent the situation encountered when screening the general population, most clinicians examine patients that have been preselected in some way. In the UK, a typical referral population has a glaucoma prevalence of at least 30%. In this setting the proportions of normal and glaucomatous eyes designated as “borderline” are more balanced. This is illustrated in Figure 3.8. The proportions of normal and glaucomatous eyes in each HRT classification group is given in Table 3.3.



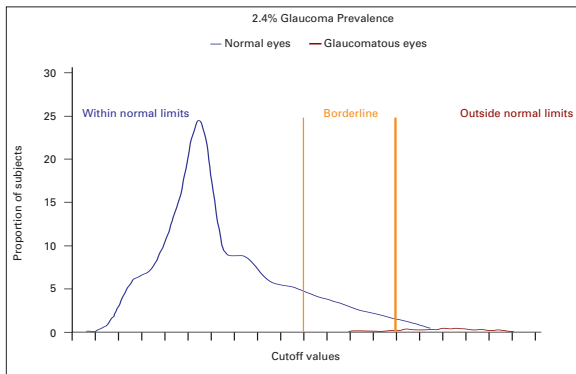
**Figure 3.5**

Plot of the global neuroretinal rim area against age in the eyes in the MRA normative database.



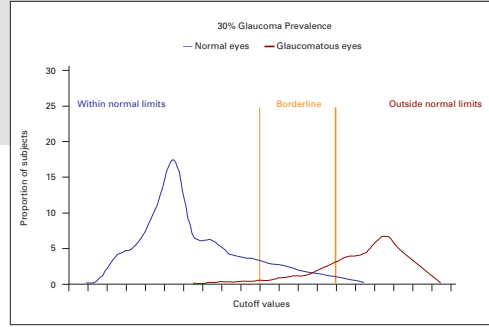
**Figure 3.6**

Plot of the distribution of normal and glaucomatous eyes at various cutoff levels of neuroretinal rim area. Note the overlap between the two.



**Figure 3.7**

Relative proportions of normal and glaucomatous eyes in the “within normal limits,” “borderline,” and “outside normal limits” classification zones for a population with a glaucoma prevalence of 2.4%.



**Figure 3.8**

Relative proportions of normal and glaucomatous eyes in the “within normal limits,” “borderline,” and “outside normal limits” classification zones for a population with a glaucoma prevalence of 30%.

**TABLE 3.1: HRT II classification of 321 normal and 283 eyes with early glaucoma.**

	Within normal limits	Borderline	Outside normal limits
Normal	79%	14%	7%
Glaucoma	14%	19%	67%

**TABLE 3.2: Proportion of eyes in each HRT classification group by true diagnosis for a glaucoma prevalence of 2.4%.**

	True normal (%)	True glaucoma (%)
HRT “within normal limits”	>99	<1
HRT “borderline”	96	4
HRT “outside normal limits”	81	19

**TABLE 3.3: Proportion of eyes in each HRT classification group by true diagnosis for a glaucoma prevalence of 30%.**

	True normal (%)	True glaucoma (%)
HRT “within normal limits”	93	7
HRT “borderline”	63	37
HRT “outside normal limits”	20	80

It can be seen from Tables 3.1 and 3.3 that the MRA greatly aids the correct classification of individual subjects. However, as with intraocular pressure measurements and visual field testing, no single test used on its own is sufficiently precise for the diagnosis of glaucoma. Thus, measurement data from all sources available (including history and examination) need to be integrated to obtain a probability of disease status. Table 3.4 illustrates the effect of taking intraocular pressure into account when interpreting the HRT classification for a population with a 2.4% glaucoma prevalence. The calculations assume a prevalence of ocular hypertension (OHT, intraocular pressure above 21 mm Hg in a nonglaucomatous eye) of 3.7%<sup>13</sup> and a prevalence of normal tension glaucoma of 40% of the glaucomatous population.

Table 3.5 gives a similar analysis for a population with a 30% prevalence of glaucoma. It can be seen from these examples that MRA findings are best interpreted in the clinical context, together with all findings of history and examination.

## NORMATIVE DATABASE

Any classification system that relies on normative data is sensitive to the composition of the normative database. It is therefore important to know how similar an individual patient is to the composition of the normative database when assessing classification results. If a patient deviates from the characteristics of subjects in the database, then the classification results should be interpreted cautiously. Important characteristics of the MRA normative database are that all subjects were white (“Caucasian ethnic group”) and with ametropia of < 6 diopters. The range of optic disc size in the database reflects that of the population from which the normal volunteers were derived, with an upper limit of around 2.80 mm<sup>2</sup>. There were also few tilted optic discs.

The MRA classification should be used cautiously in subjects that are nonwhite, although a recent publication has demonstrated similar specificity of MRA in black and white Americans.<sup>14</sup> Racial differences in normative values may necessitate ethnic-specific cutoffs to optimize disease detection strategies.

Disc size is taken into account in MRA. However, some residual effect of disc size on classification remains,<sup>12</sup> and the MRA classification in discs larger than 2.80 mm<sup>2</sup> may be less specific. Care should also be taken in assessing eyes with a high refractive error, or that have marked disc tilt. Heidelberg Engineering is currently expanding the HRT II normative database to include more normal subjects from a wide range of ethnic backgrounds and to increase the range of optic disc size. If differences in the neuroretinal rim/optic disc size relationship are found between different ethnic groups, then ethnicity-specific normative databases will be derived.

In the same way that certain features may give rise to a false-positive classification of a normal ONH (such as a large ONH), certain features of glaucomatous ONHs may give rise to false-negative classification. The most frequent of these is shallow cupping in the presence of marked parapapillary atrophy. In these cases the optic disc is often clearly abnormal on the clinical examination.

False-negative and false-positive classification may occur if the ONH margin (contour line) is incorrectly drawn. The ONH margin is defined as the inner margin of the scleral ring of Elschnig.

**TABLE 3.4:** The proportion of subjects with true glaucoma, with and without OHT, in each HRT classification group for a population with a 2.4% glaucoma prevalence.

	<b>With OHT (%)</b>	<b>Without OHT (%)</b>
<b>HRT “within normal limits”</b>	7	<1
<b>HRT “borderline”</b>	35	1
<b>HRT “outside normal limits”</b>	79	9

**TABLE 3.5:** The proportion of subjects with true glaucoma, with and without OHT, in each HRT classification group for a population with a 30% glaucoma prevalence.

	<b>With OHT (%)</b>	<b>Without OHT (%)</b>
<b>HRT “within normal limits”</b>	55	3
<b>HRT “borderline”</b>	90	19
<b>HRT “outside normal limits”</b>	99	63

## OPTIC DISC / VISUAL FIELD TOPOGRAPHIC RELATIONSHIP

A particular advantage of MRA is the sectoral nature of the analysis, so that it is possible to compare the sectoral neuroretinal rim area (length of the green bar in relation to the prediction intervals) to the corresponding regions of the visual field on the basis of known anatomy.<sup>15</sup> Figure 3.9 illustrates the correspondence between the HRT predefined segments and the visual field.

Figure 3.10 illustrates an example of a 67-year-old subject with ocular hypertension who developed an infero-temporal notch in the optic disc with corresponding superior paracentral arcuate visual field loss.

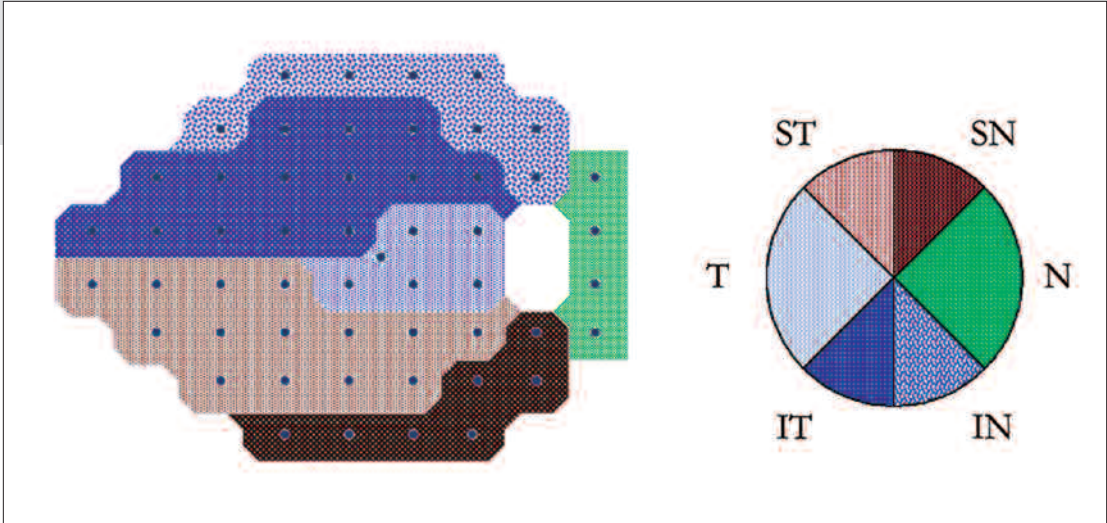
## CONCLUSION

Moorfields Regression Analysis provides clinically useful information regarding the topography of the optic disc in comparison to a normative database and aids the correct classification of individual patients. The appearance of the optic disc and the results of this analysis should be evaluated in the context of the clinical examination and tests of visual function.

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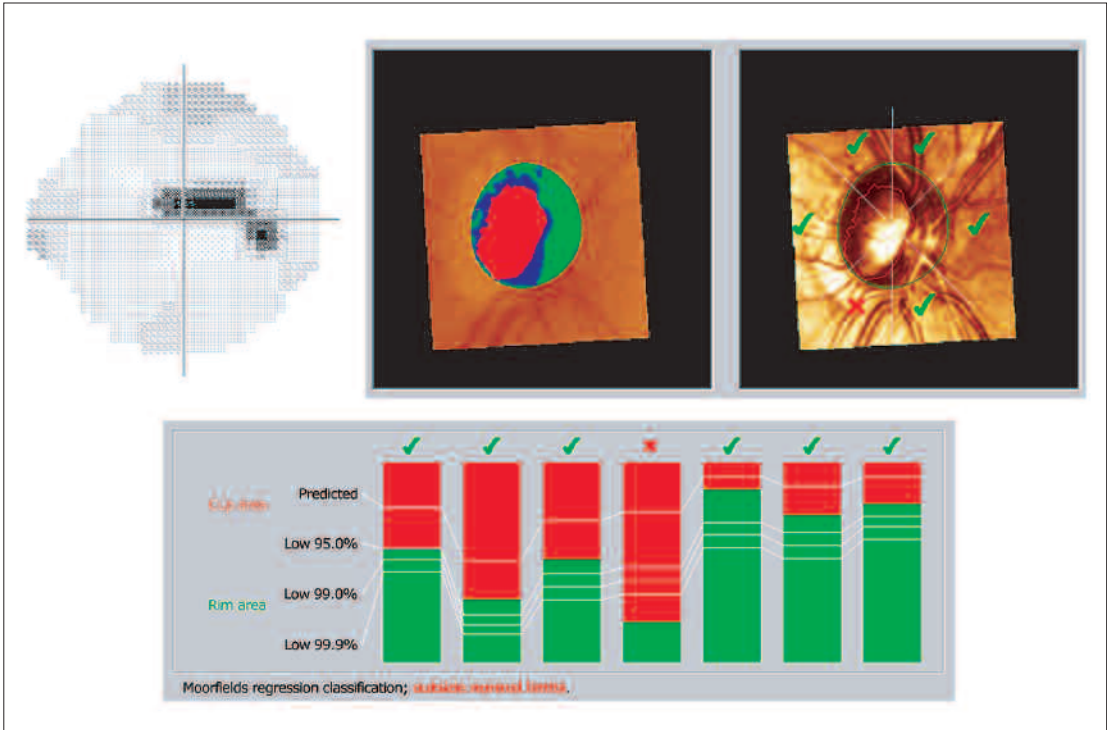
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**Figure 3.9**  
 The Humphrey 24-2 visual field grid for a right eye divided into regions that correspond with the HRT II predefined ONH sectors.

(T = Temporal, ST = Supero-temporal, IT = Infero-temporal, N = Nasal, SN = Supero-nasal, IN = Infero-nasal)



**Figure 3.10**  
 Visual field gray scale and HRT II software analysis of an image acquired with the HRT. The infero-temporal segment of the ONH is clearly outside normal limits, and the reflectivity image demonstrates that the loss of the neuroretinal rim is on the temporal side of the infero-temporal segment. This corresponds with the location of visual field loss.