Objective: To determine whether the ISNT rule (that normal eyes have a characteristic configuration for disc rim thickness of inferior ≥ superior ≥ nasal ≥ temporal), widely used for clinical evaluation of the optic nerve head, can differentiate normal from glaucomatous eyes.

Methods: All subjects underwent complete eye examination, including achromatic automated perimetry, simultaneous stereoscopic disc photography, and confocal scanning laser ophthalmoscopy. Subjects with normal eyes had no evidence of glaucoma or ocular hypertension and had normal perimetry measurements. Subjects with glaucoma had a reproducible visual field defect. One eye from each subject was randomly enrolled. The ISNT rule was assessed by masked evaluation of disc photographs at the 3, 6, 9, and 12 o’clock positions.

Results: Sixty-six subjects with normal eyes (33 black and 33 white individuals) and 43 with open-angle glaucoma (15 black and 28 white individuals) were enrolled. The ISNT rule was intact in 52 (79%) of 66 normal eyes and 12 (28%) of 43 glaucomatous eyes (P<.001). Multiple logistic regression indicated that the odds ratio for glaucoma associated with violation of the ISNT rule was 6.04 (95% confidence interval, 1.74-20.95) after adjustment for age; race was not a confounder of this association.

Conclusion: The ISNT rule is useful in differentiating normal from glaucomatous optic nerves and is unaffected by race.

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optical disc appearance based on clinical examination, and normal automated achromatic perimetry results. Absence of glaucomatous optic neuropathy was defined as a vertical cup-disc asymmetry between eyes of less than 0.2, a cup-disc ratio of 0.6 or less, and an intact neuroretinal rim without notching or excavation. A normal visual field had a pattern standard deviation within the 95% normal limits and a glaucoma hemifield test result within the 99% normal limits on a reliable visual field.

Subjects with glaucoma had open angles on gonioscopy and adherence to the ISNT rule while adjusting for covariates. Multiple logistic regression analysis was used to investigate the association between glaucoma and adherence to the ISNT rule while adjusting for covariates. P < 0.05 was considered statistically significant. Results are presented as mean ± SD unless otherwise indicated.

One hundred nine eyes of 109 subjects were enrolled. Sixty-six (33 white and 33 black) subjects were used as normal controls and 43 (28 white and 15 black) had glaucoma. Patient demographic and ocular characteristics are described in Tables 1, 2, and 3. Subjects with normal eyes were younger than those with glaucoma (46.1 ± 13.6 vs 61.3 ± 10.7 years; P < .001) (Table 1). Sex distribution (P = .55) and refractive error (P = .37) were similar between the 2 groups. Normal eyes had a shorter axial length than eyes with glaucoma (23.6 ± 0.9 vs 24.1 ± 1.1 mm; P = .01).

The ISNT rule was intact in 52 (79%) of 66 normal eyes and 12 (28%) of 43 glaucomatous eyes (P < .001) (Table 1). Among subjects with normal eyes, the proportion of subjects adhering to the ISNT rule did not differ by race (25 [76%] of 33 black subjects vs 27 [82%] of 33 white subjects; P = .76 by Fisher exact test) (Table 2). Among white participants, the ISNT rule was intact more often in normal eyes (27/33 [82%]) than in glaucomatous eyes (10/28 [36%]) (P < .001) (Table 3). Similarly, among black participants, the ISNT rule was intact in 25 (76%) of 33 normal eyes compared with 2 (13%) of 15 glaucomatous eyes (P < .001) (Table 3). The odds ratio (OR) for glaucoma associated with violation of the ISNT rule in black participants (OR, 20.3; 95% confidence interval [CI], 3.7-110.0) exceeded that in whites (OR, 8.1; 95% CI, 2.5-26.2), but the sample sizes were small and Breslow-Day test results indicated that the ORs were not significantly different, suggesting that race was a confounder and not an effect modifier.

Of the 14 normal eyes that violated the ISNT rule, 7 had an inferior rim that was thinner than the superior rim. Of the remaining 7 eyes, 5 had a nasal rim that was thicker than the inferior rim and 2 had a temporal rim thicker than the inferior rim and 2 had a temporal rim.

### Table 1. Patient Demographics and Ocular Findings by Diagnosis Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Eyes</th>
<th>Glaucomatous Eyes</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>66</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>46.1 ± 13.6</td>
<td>61.3 ± 10.7</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Range</td>
<td>19 to 77</td>
<td>43 to 82</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 (62%)</td>
<td>24 (56%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (38%)</td>
<td>19 (44%)</td>
<td></td>
</tr>
<tr>
<td>Refractive error, mean ± SD, diopters</td>
<td>-0.3 ± 1.4</td>
<td>-0.6 ± 2.0</td>
<td>.37†</td>
</tr>
<tr>
<td>Range</td>
<td>-5.0 to 2.8</td>
<td>-5 to 3.5</td>
<td></td>
</tr>
<tr>
<td>Axial length, mean ± SD, mm</td>
<td>23.6 ± 0.9</td>
<td>24.1 ± 1.1</td>
<td>.01†</td>
</tr>
<tr>
<td>Range</td>
<td>21.7 to 25.7</td>
<td>22.6 to 26.9</td>
<td></td>
</tr>
<tr>
<td>Average visual field measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean deviation, dB</td>
<td>-0.58</td>
<td>-5.08</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Range</td>
<td>-6.80 to 1.56</td>
<td>-25.32 to 1.49</td>
<td></td>
</tr>
<tr>
<td>Pattern standard deviation, dB</td>
<td>1.61</td>
<td>4.85</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Range</td>
<td>1.00 to 6.55</td>
<td>1.39 to 14.29</td>
<td></td>
</tr>
<tr>
<td>Disc area, mean ± SD, mm²</td>
<td>1.82 ± 0.40</td>
<td>2.27 ± 0.60</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Range</td>
<td>0.95 to 2.91</td>
<td>1.49 to 3.82</td>
<td></td>
</tr>
<tr>
<td>ISNT rule intact, No. (%)</td>
<td>52 (79%)</td>
<td>12 (28%)</td>
<td>&lt;.001‡</td>
</tr>
</tbody>
</table>

Abbreviation: ISNT, for normal disc rim thickness, inferior ≥ superior ≥ nasal ≥ temporal.

*Unpaired, 2-tailed t test.
†Fisher exact test.
‡Bonferroni’s correction for multiple comparisons.

![Figure](https://via.placeholder.com/150)

**Figure.** Clinical assessment of the ISNT rule for a normal optic nerve. The ISNT rule is that disc rim thickness shows a characteristic configuration of inferior (I) greater than or equal to superior (S) greater than or equal to nasal (N) greater than or equal to temporal (T) (or I=S=N=T).

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that was thicker than the superior rim. Analysis of the vertical rim alone by diagnostic group demonstrated that the inferior rim was generally thicker than or equal to the superior rim for both normal (59/66 [89%]) and glaucomatous (26/43 [60%]) eyes. This difference between the groups was statistically significant (P < .001).

Black subjects with glaucoma in our study were significantly more myopic and had eyes with greater axial length compared with black subjects with normal eyes (P = .03 and P < .001 for refractive error and axial length, respectively) (Table 3). This difference was not seen in white subjects (P = .64 and P = .70 for refractive error and axial length, respectively) (Table 3).

The mean optic disc area measured by confocal scanning laser ophthalmoscopy was significantly larger in subjects with glaucoma (P < .001). The mean optic disc area was 1.82 ± 0.40 mm² (range, 0.95-2.91 mm²) in subjects with normal eyes and 2.27 ± 0.60 mm² (range, 1.49 to 3.82 mm²) in those with glaucoma (Table 1).

Multiple logistic regression analysis was performed to examine the relationship between the diagnosis of glaucoma and the ISNT rule while adjusting for potential confounders. We found significant associations of glaucoma diagnosis with violation of the ISNT rule (OR, 6.04; 95% CI, 1.74-20.95; P = .005), larger disc area (OR, 10.75; 95% CI, 2.33-49.67; P = .002), and increasing axial length (OR, 2.55; 95% CI, 1.21-5.35; P = .01) after adjusting for potential confounding due to age and race.

To achieve greater homogeneity of age between the subjects with normal eyes and those with glaucoma, we further analyzed the data, restricting the subject population to 69 individuals aged 43 to 66 years. This in-

Table 2. Patient Demographics and Ocular Findings by Race and Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Eyes</th>
<th>Glaucmatous Eyes</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes, No.</td>
<td>Black</td>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>33</td>
<td>28</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>Female</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Refractive error, mean ± SD, diopters</td>
<td>20 (61)</td>
<td>13 (39)</td>
<td>.60‡</td>
</tr>
<tr>
<td>Axial length, mean ± SD, mm</td>
<td>20 (61)</td>
<td>13 (39)</td>
<td>.21‡</td>
</tr>
<tr>
<td>Average visual field measures</td>
<td>23.7 ± 1.0</td>
<td>23.8 ± 1.0</td>
<td>.70‡</td>
</tr>
<tr>
<td>Mean deviation, dB</td>
<td>-0.50</td>
<td>-3.53</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Pattern standard deviation, dB</td>
<td>1.63</td>
<td>3.73</td>
<td>.002‡</td>
</tr>
<tr>
<td>Disc area, mean ± SD, mm²</td>
<td>1.79 ± 0.40</td>
<td>2.10 ± 0.50</td>
<td>.01†</td>
</tr>
<tr>
<td>ISNT rule intact, No. (%)</td>
<td>25 (76)</td>
<td>10 (36)</td>
<td>&lt;.001‡</td>
</tr>
</tbody>
</table>

Table 3. Patient Demographics and Ocular Findings by Race and Diagnosis Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White</th>
<th>Black</th>
<th>P Value*</th>
<th>White</th>
<th>Black</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>35.0 ± 12.8</td>
<td>45.0 ± 12.8</td>
<td>&lt;.001†</td>
<td>47.0 ± 14.6</td>
<td>55.8 ± 8.2</td>
<td>.04†</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractive error, mean ± SD, diopters</td>
<td>21 (64)</td>
<td>6 (40)</td>
<td>.60‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial length, mean ± SD, mm</td>
<td>23.7 ± 1.0</td>
<td>23.8 ± 1.0</td>
<td>.21‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average visual field measures</td>
<td>23.5 ± 0.9</td>
<td>23.8 ± 1.0</td>
<td>.70‡</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean deviation, dB</td>
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<td>&lt;.001‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ISNT, for normal disc rim thickness, interior nasal temporal.
*Comparing black and white subjects in each diagnostic group.
†Unpaired, 2-tailed t test.
‡Fisher exact test.
cluded 39 subjects with normal eyes (17 black and 22 white individuals, median age [range], 52 [43-60] years) and 30 subjects with open-angle glaucoma (14 black and 16 white individuals, median age [range], 55 [43-60] years). Median ages did not differ significantly between the 2 groups (P = .14). The ISNT rule was intact in 32 (82%) of 39 normal eyes and 8 (27%) of 30 glaucoma-
tous eyes (P < .001). In multiple logistic regression mod-
ing adjusted for age and race, we found significantly
elevated ORs for glaucoma associated with violation of
the ISNT rule (OR, 7.8; 95% CI, 2.1-28.6) and larger disc
size (OR per unit increase, 15.0; 95% CI, 2.5-89.7).

The ISNT rule was originally described by Jonas et al,2 who
used rim area measurements of normal eyes, calculated from
projected optic disc photographs. Later, retinal nerve fi-
er layer thickness was measured at the optic disc borders
histomorphometrically and was found to follow the same
rule.3 This morphometric characteristic is not followed in
patients with glaucoma.4 The present study confirms the
work of Jonas et al5,6 and the utility of the ISNT rule in clin-
cal practice in black and white subjects.

Several studies6-8 have demonstrated a higher preva-
lence of open-angle glaucoma with higher rates of blind-
ness in persons of black African ancestry compared with
European-derived populations. Racial differences in ocu-
ar anatomy include larger disc and cup areas in black
subjects6-10 with similar neuroretinal rim area, yielding
an overall larger cup-disc ratio.11 Girkin et al12 reported
that most differences in optic disc topography between
black and white subjects with normal eyes became non-
significant after adjustment for reference plane height and
for optic disc area as measured by confocal scanning la-
sar ophthalmoscopy. Girkin and colleagues10 also dem-
onstrated that racial differences in optic disc structure
had little impact on the relative ability of subjective and
objective methods to discriminate between glaucoma-
tous and normal optic discs. One could therefore expect
the neural rim to follow the ISNT rule regardless of race.
In the present case study, race and age were treated as
potential confounders, and multivariable logistic regres-
sion techniques were used to control for the potential ef-
fects of imbalances in these variables between groups.

The nasal sector of the optic nerve is more difficult to
evaluate owing to obscuration of the rim by the exit of
large retinal vessels. We tested the hypothesis that the inferior-superior rim relationship alone would simplify
the detection of a suspicious optic disc. However, this
turned out not to be the case. In future studies, evalua-
tion of the temporal disc region compared with the other
3 rim sectors may increase specificity in detecting glau-
comatous optic discs because the vertical rim is fre-
quently affected before the horizontal rim.

Several studies15-17 have found equal optic disc sizes
in both normal and glaucomatous eyes, while others18 have
demonstrated larger disc areas in glaucomatous eyes. Op-
tic disc area in the present study was greater in the glau-
comatous eyes than in the normal eyes for both races,
as well as in the combined racial group. The ISNT rule re-
mained a predictor of a glaucoma diagnosis after con-
trolling for multiple factors including disc area.

Despite the fact that there is axonal loss with age, it re-
mains controversial whether age affects the neuroretinal
rim area.14,21,22 It is unlikely that the greater age of the pa-
tients with glaucoma significantly affected the relative rim
thickness at the different locations. In the multivariate anal-
ysis on the age-matched groups (n = 69), the ISNT rule kept
its diagnostic ability in detecting glaucoma.

The present study has several limitations. The sample
size is relatively small, and in a larger cohort violation of
the ISNT rule could be correlated with visual field sta-
tus and disease severity. Although glaucoma was de-
finied strictly based on functional criteria, in the evalu-
ation of normal eyes we could not avoid the inclusion of
optic nerve information typically obtained during a rou-
tine eye examination. One could argue that this bias would
favor inclusion of normal eyes that adhere to the ISNT
rule, yet the fact that more than 20% of our normal eyes
violated the ISNT rule suggests that this potential bias
was minimal. The reality of glaucoma structure and func-
tion research is that the visual field, intraocular press-
sure, and optic disc are always examined in every pa-
tient entering any imaging or visual function study. Our
definition of normal eyes used previously published stan-
dard criteria that include an optic disc examination in
addition to functional testing.23-25 We intentionally ex-
cluded glaucoma suspect eyes and eyes with preperimet-
ric glaucoma to facilitate the comparison between nor-
mal and glaucomatous eyes. Future studies should address
the use of the ISNT rule for these individuals. Finally,
our results can be applied only to patients with a similar
range of refractive error.

The present study suggests that the ISNT rule is a clini-
cally useful method to aid in glaucoma diagnosis and risk
assessment in clinical practice. Although differences in
optic nerve anatomy exist between black and white sub-
jects, our results suggest that the ISNT rule can be ap-
plied equally to white and black individuals.

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firmary, 310 E 14th St, Suite 304, New York, NY 10003
(jml18@earthlink.net).

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Previous Presentation: This study was presented in part at
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sion and Ophthalmology; May 5, 2005; Fort Lauderdale, Fla.

REFERENCES