Glaucoma Risk – Correlations between Measurements from Optical Coherence Tomography and Ocular Response Analyzer

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Abstract— **Glaucoma can lead to blindness if it is not diagnosed in time. To detect it in a patient, a complex assessment is necessary, including: intraocular pressure (IOP) measurements and detection of its influence upon the optic nerve. Our work is based on the hypothesis that retinal nerve fiber layers (RNFL) are influenced by IOP and corneal properties. First, investigations were made with the Reichert Ocular Response Analyzer (ORA) for the intraocular pressure (Goldman- correlated Intraocular Pressure: IOPg, Compensated Intraocular Pressure: IOPc) and corneal properties (Corneal Hysteresis: CH, specific damping capacity: φ). Then patients were measured with Optical Coherence Tomography (OCT) for retinal nerve fiber layers thickness: average and superior, inferior, temporal, nasal quadrants. The unified database comprises all these data collected from 4343 eyes and its construction was based on a text extraction method that uses image processing, optical character recognition (OCR) and virtual instrumentation techniques. Appropriate technical data (ORA, OCT) collected, properly computed and judged are very useful in glaucoma diagnosis and management, which is demonstrated in one of the largest databases studied (more than 4,000 eyes measured).**

Keywords— **intraocular pressure, ocular response analyzer, optical coherence tomography, retinal nerve fiber layer, optical character recognition**

I. Introduction

From the early 1880's until the last quarter of the 20th century, glaucoma was defined as "pressure within the eye higher than the statistical normal of the population." It was believed that this elevated intraocular pressure (IOP) would cause a certain type of damage to the optic nerve, which would eventually cause blindness if left untreated.

The American Academy of Ophthalmology now defines glaucoma as "a group of diseases with certain features including an intraocular pressure that is too high for the continued health of the eye." Glaucoma can be regarded as a group of diseases that have as a common end-point a characteristic optic nerve damage which is determined by both structural change and functional deficit [1].

In order to quantify in a patient the risk of glaucoma, first it's necessary to measure at least two important parameters: intraocular pressure and optic nerve characteristics (structure and function), and then integrate the collected data with the rest of the clinical data.

II. Work Hypothesis

Glaucoma is a leading cause of irreversible blindness throughout the world. The common denominator of the glaucoma is a characteristic optic neuropathy, which derives from various risk factors including Intraocular Pressure (IOP). Although elevated IOP is clearly the most frequent causative risk factor for glaucomatous optic nerve atrophy, it is not the only factor, and attempts to define glaucoma on the basis of ocular tension are no longer advised.

It has been demonstrated that corneal biomechanical properties influence the results and outcomes of various ocular measurements and procedures, and may hold clues to diagnosing and managing ocular diseases [2].

It's crucially important, therefore, to quantify in some way the influence of the mentioned factors upon the optic nerve.

The correlation between the most important factors in diagnosis and evaluating a glaucoma suspect patient were studied: *Intraocular Pressure* (IOP) - as a risk factor, *corneal biomechanical properties* - as modulating factors upon IOP's influence on the optic nerve and *retinal nerve fiber layers* (RNFL) - as a measure of the optic nerve damage in glaucoma suspects patients.

III. Methods

A database was built, where the measured parameters from 4383 eyes were collected. Only 4343 of them, with valid data, were used in the statistical research. The investigations took place during the years 2006-2012. Every patient carried out the following investigations: intraocular pressure and corneal properties with Reichert Ocular Response Analyzer (ORA), retinal nerve fiber layers with Optical Coherence Tomography (OCT).

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A. Ocular Response Analyzer Data

The Reichert Ocular Response Analyzer utilizes a dynamic bi-directional applanation process to measure the biomechanical properties of the cornea and the intraocular pressure of the eye. The basic output of the measurement process is a Goldman - correlated intraocular pressure measurement (IOPg), and a measure of corneal tissue properties called Corneal Hysteresis (CH), which is the result of viscous damping in the corneal tissue. The CH measurement also provides a basis for a new additional parameter: Corneal Compensated Intraocular Pressure (IOPcc), frequent different from IOPg. IOPcc is an Intraocular Pressure measurement that is less affected by corneal properties than other methods of tonometry, such as Goldman. Human corneal tissue is a complex *viscous-elastic* structure. The CH measurement is an indication of viscous damping in the cornea. The subjects whose corneas exhibit low CH, which can be thought of in simple terms as a "soft" cornea, are probable candidates for a variety of ocular diseases [3]. The specific corneal damping capacity (φ) is calculated using relation (1).

$$\varphi = \frac{D}{U} = \frac{CH}{2 \cdot IOPg} \tag{1}$$

The specific damping capacity (φ) is defined as the energy loss per cycle (D) divided by the peak energy stored (U), which for the being considered spring mass system is the energy stored in the spring at maximum deflection [4].

B. Optical Coherence Tomography Data

Optical Coherence Tomography (OCT) performs high-resolution, micron-scale, cross-sectional, or tomography imaging of the eye internal microstructure. OCT enables real-time in situ imaging of tissue structure with resolution of 3 to 15 microns, which are 10 times to 100 times higher than conventional clinical imaging technologies such as ultrasound, magnetic resonance or computer tomography. OCT measurement beam is in the infrared, no ionizing radiation, so imaging is well tolerated by patients [5].

To search for optic nerve damage in a patient a structural eye parameter was used in this study: Retinal Nerve Fiber Layers (RNFL) that was measured with Stratus 3000 - Carl Zeiss Optical Coherence Tomography (OCT). To measure RNFL: circular scans were obtained with a diameter of 3.4 mm centered on the optic disk [6]. The scan was initiated at clock dial 9:00 and proceeded clockwise (Figure 1). The mean RNFL thickness values were automatically calculated globally and separately for the superior, inferior, temporal, and nasal quadrants (90 degrees each) using OCT software version A5 (Humphrey-Zeiss Medical Systems).

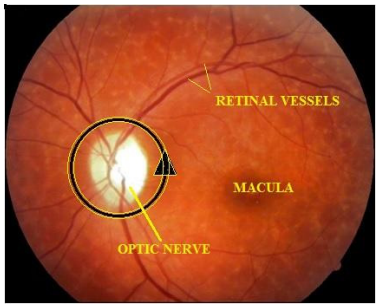

Fig. 1 RNFL circumpapillary scan type (black arrow - around optic nerve head) represented on an ocular fundus image (with macula, optic nerve and retinal vessels marked)

Two different parameters were collected from the "pdf" file with the scan results (OCT printout - in Figure 2). The first was the mean RNFL thickness of the entire circumference of the optic disk, labeled as "fiber avg" in database. The second parameter was quadrant thickness of RNFL, labeled as "fiber S", "fiber I", "fiber T" and "fiber N" - for superior, inferior, temporal respectively nasal quadrants.

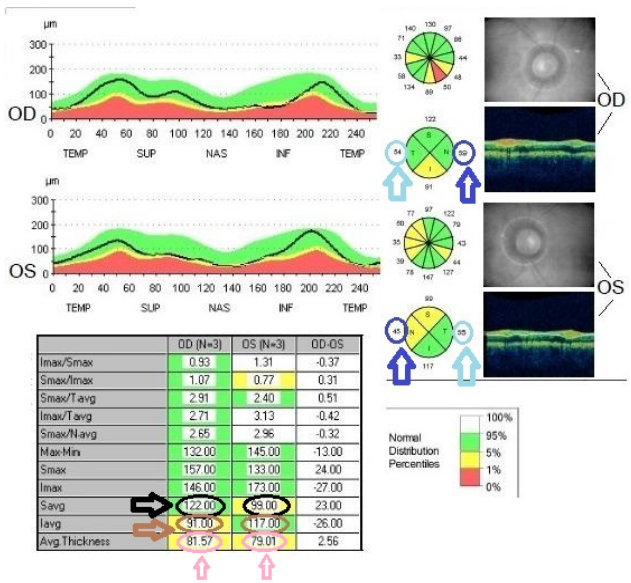

Fig. 2 OCT printout –PDF file

OCT printout reveals the appearance of RNFL scan and automated analysis for both eyes (right eye and left eye, labeled as OD/OS). The collected data from the OCT printout, that are integrated in the final database, are marked with circles and arrows of different colors for different quadrants, as in Fig2: light blue for temporal quadrants (labeled as "fiber T"), indigo for nasal quadrants (labeled as "fiber N"), black for superior quadrants ("fiber S"), brown

for inferior quadrants ("fiber I"), pink for average thickness of RNFL ("fiber avg"). Each eye from a patient was considered and analyzed separately in the database, because of various differences between right and left eye regarding IOP, corneal properties and possibility in a patient to have optic nerve damage / secondary glaucoma only in one eye.

C. Building the Integrated Database

In order to achieve clinical a research goal in ophthalmologists practice the extraction of the relevant information from different types of documents become one of the most important. Biomedical information exists in form like: text, journal articles, databases or electronic health records [7]. The OCT device from Review Ophthalmological Center gives the patients results in "pdf" documents and ORA device gives the results in "csv" files. In order to extract the necessary information and to build an integrated database a set of virtual instruments (vi) in Labview (National Instruments) were implemented.

For required OCT data, the "pdf" files (Figure 2) were converted in "tiff" files. By using the NI Vision Assistant and NI Vision Development Module an optical character recognition (OCR) based application was implemented (Figure 3) [8].

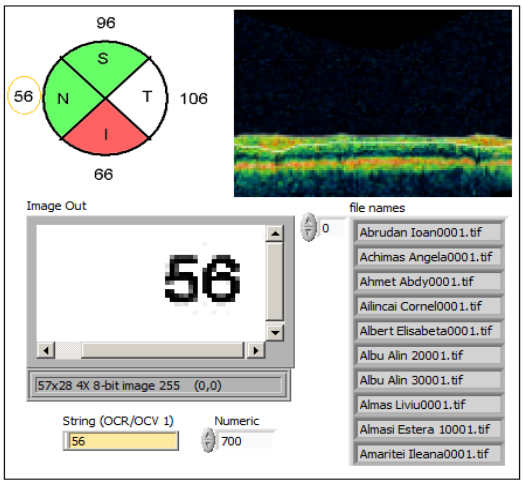

Fig. 3 The application for ORA data retrieval-The vi. front panel

For each feature the values were determined after some image enhancement algorithms: low pass filter for smoothing, Look Up Table (LUT) –exponential for contrast or masking for select the region of interest (ROI). Finally, after the OCR session the characters set were read.

The collected data from ORA and OCT were put together and exported in an "excel" file, wherefrom 4343 eyes values were available to be statistically computed.

The built integrated database that is used finally for the statistical analysis contains for each eye the next features: The gender and the age of the patient, Goldman - correlated Intraocular Pressure (IOPg), Compensated Intraocular Pressure (IOPcc), Corneal Hysteresis (CH), Corneal Resistance Factor (CRF), computed specific damping capacity (φ), retinal nerve fiber layers thickness - as a mean ("fiber avg") and the average measurements for each of the four quadrants ("fiber S, I, T and N") around the optic nerve (Figure 2).

For statistical analyze of data SPSS version 13.0.1 was used, with descriptive statistics, bivariate correlation, linear regression and multiple stepwise regression statistics procedures.

Database from the "excel" file was imported as a "sav" file in SPSS to be studied. First an overview was made and the main features of the collected data were analyzed. The correlation indices (Pearson and Spearman) were computed, to see the *strength* of association between variables. Multiple stepwise regression analysis was used to *quantify* different associations. This study was made because all previous studies show that IOP (for example) produces a RNFL thickness decreasing [1], [5], [14], and the goal is to know which variables or association are more related with this RNFL loss.

IV. Experimental Results

The 4343 studied eyes are coming from a group of patients with ages are distributed between 8 and 95 years, with a mean of 53.17 years old and a standard deviation of 17.46 years old (Figure 4). The gender distribution was: 1572 male and 2771 female.

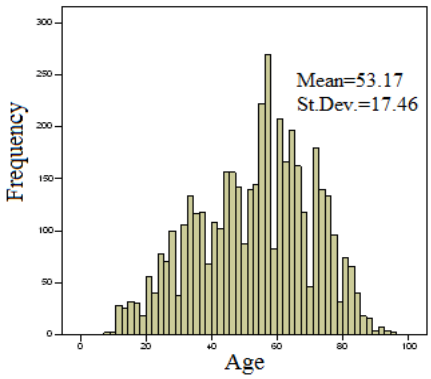

Fig. 4 The frequency of studied patients (4343) grouped according to age

Descriptive statistics on our database revealed: Goldman - correlated Intraocular Pressure (IOPg) between 4.1 and 65.9 mmHg, Compensated Intraocular Pressure (IOPcc) between 6.2 and 70.7 mmHg, Corneal Hysteresis (CH)

between 0 and 26.6 , Corneal Resistance Factor (CRF) with values between 3.4 and 27, computed specific damping corneal capacity (φ) between 0 and 1.195, retinal nerve fiber layers thickness - as an average around the optic nerve (fiber avg) between 23.96 - 150.20 microns and the measurements for each of the four quadrants around the optic nerve (fiber S, N, T, I) respectively 9 - 191, 10 - 174, 15-175, 1-199 microns as minimum - maximum measurements (Table 1).

Table 1 Descriptive statistic of the database in study

	N	Minimum	Maximum	Mean	Std. Deviation
Fiber-S	4343	9	191	124.06	22.972
Fiber-N	4343	10	174	79.96	19.154
Fiber-T	4343	15	175	70.84	14.854
Fiber-I	4343	1	199	124.29	22.653
Fiber -Avg	4343	23.96	150.20	99.804	15.060
IOPg	4343	4.1	65.9	18.356	5.0162
IOPc	4343	6.2	70.7	18.974	5.3419
CRF	4343	3.4	27.5	10.851	2.0794
CH	4343	.0	26.6	9.913	2.1272
φ	4343	.000	1.195	.291	.1022
Valid N (listwise)	4343				

Correlations between age and RNFL thickness (average and the four quadrants) with the other measured parameters: IOP, corneal properties and φ were computed (Table 2).

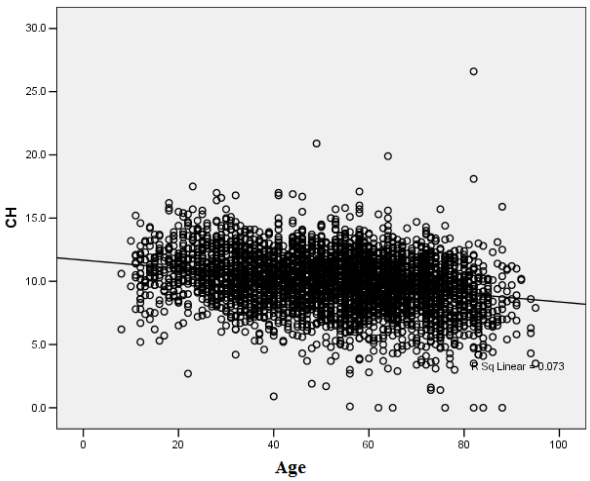

Fig. 5 Regression scatterplot for CH dependence on age

The regression scatterplot for CH negative linear relation by age is illustrated in Fig. 5: CH is decreasing with the increasing age (r = - 0.271). The regression constant (point at which the regression line would hit the vertical axis of the graph) is 11.67 (CH value for age 0); Regression unstandardized coefficient is -0.033. It is therefore a possibility to predict CH by knowing the age by using the relation (2)

$$CH = 11.67 - 0.033 \times age \quad (2)$$

Statistically significant correlations for all studied variables were found with the exception of those between temporal RNFL and IOPg and CRF; some of them are positive (RNFL is decreasing when the studied parameter - CH, CRF, φ - is decreasing) and others are negative (RNFL is decreasing when the studied parameter - IOPg and IOPc - are increasing). In Table 2 the most significant correlations between age and the measured or computed parameters are included; they are sorted in decreasing order by statistical relevance; RNFL thickness and corneal parameters decrease with the age (negative correlations); IOPg and especially IOPc increase with the age.

Table 2 Pearson and Spearman correlation coefficients (ordered decreasing by clinical relevance) and their statistical significance for the most significant correlations detected between age, RNFL ("fiber" avg, I, S, N, T), intraocular pressure (IOPg, IOPc), corneal parameters (CH, CRF and φ)

Studied Variables		Pearson correl. coeff.	Statistic. signific. (p)	Spearman correl. coeff.	Statistic. signific. (p)
age	fiber avg	-0.322	0.000	-0.331	0.000
age	fiber S	-0.313	0.000	-0.324	0.000
age	CH	-0.271	0.000	-0.261	0.000
age	fiber I	-0.244	0.000	-0.236	0.000
age	φ	-0.204	0.000	-0.224	0.000
age	IOPc	0.203	0.000	0.098	0.000
age	fiber T	-0.191	0.000	-0.204	0.000
age	fiber N	-0.188	0.000	-0.206	0.000
age	CRF	-0.167	0.000	-0.150	0.000
fiber avg	CH	0.165	0.000	0.136	0.000
fiber avg	IOPc	-0.162	0.000	-0.130	0.000
fiber I	IOPc	-0.160	0.000	-0.127	0.000
fiber I	CH	0.157	0.000	0.129	0.000
fiber avg	φ	0.150	0.000	0.141	0.000
fiber S	CH	0.150	0.000	0.0123	0.000
fiber I	φ	0.148	0.000	0.137	0.000
fiber S	IOPc	-0.139	0.000	-0.139	0.000
fiber S	φ	0.125	0.000	0.115	0.000
fiber I	IOPg	-0.114	0.000	-0.084	0.000
fiber avg	IOPg	-0.112	0.000	-0.084	0.000
fiber N	φ	0.104	0.000	0.115	0.000

Multiple stepwise regressions revealed the influence of different associations between the collected parameters, and show which of these associations are better to predict RNFL loss in glaucoma suspect patients. (Table 3)

The best predictors, with negative correlation, are associations: age + IOPc, age+ CH, Age+ φ (Beta = -0.3, multiple R= 0.11), but they still only account for 11% of RNFL variability. Considering different association for age, IOP, CH correlation coefficients are increasing significant (Beta = -0.34 for IOPg+IOPc, -0.39 for IOPg+IOPc+CH comparative with -0.322 for age) so their increase is a better predictor for RNFL loss, than any other studied parameter considered alone.

Table 3 Multiple regression stepwise, with different predicting variable association, considering "Fiber avg" as Dependent variable (the most significant correlations are highlighted)

Dependent Variable: Fiber -Avg		Unstandardized coefficients		Standardized Coefficients		
Variable	R^2	B	standard error b	Beta	t	Signif. of t
IOPg	0.013	-0.33	0.045	-0.112	-7.426	0.000
IOPg,	0.033	0.59	0.106	0.198	5.594	0.000
IOPc		-0.96	0.100	-0.342	-9.655	0.000
IOPg,	0.033	0.71	1.825	0.238	0.392	0.695
IOPc,		-1.10	2.114	-0.391	-0.522	0.602
CH		-0.15	2.295	-0.021	-0.066	0.947
IOPg,	0.115	-0.17	1.790	-0.056	-0.095	0.925
IOPc,		-0.16	2.057	-0.057	-0.078	0.938
CH,		0.51	2.261	0.072	0.225	0.822
φ,		-7.80	5.421	-0.053	-1.439	0.150
age		-0.26	0.013	-0.297	-19.97	0.000
Age	0.104	-0.28	0.012	-0.322	-22.41	0.000
Age, φ	0,111	-0.26	0.013	-0.304	-20.81	0.000
		12.95	2.153	0.088	6.013	0.000
Age,	0.110	-0.26	0.013	-0.299	-20.12	0.000
CH		0.60	0.105	0.084	5.651	0.000
Age,	0.115	-0.26	0.013	-0.297	-19.96	0.000
CH,		0.50	0.107	0.070	4.600	0.000
IOPg		-0.20	0.044	-0.067	-4.594	0.000
Age,	0.114	-0.26	0.013	-0.302	-20.71	0.000
IOPc		-0.29	0.041	-0.103	-7.062	0.000

V. Discussions

There are many parameters to look for when we try to distinguish between a normal and a glaucomatous patient. The variability between individuals and within an individual over a lifetime make difficult to appreciate the situation of a patient at one moment. Biomechanical properties of the eye structures, measured by ORA are very important to assess a glaucoma suspect, and there are many studies focused on these properties [9]. By now nearly everyone recognizes that the current gold standard for measuring IOP, the Goldmann tonometer, has considerable flaws. The IOP measure is affected by corneal properties including rigidity, thickness, structure, hydration curvature and perhaps other factors not yet identified. ORA is capable to provide pressure measurements that are less affected by corneal properties, and give us additional information. All of these were taken into account and they determine us to make a step on ward to introduce these data into our daily medical practice.

Recent studies [10] shows that IOP induce a certain amount of stress and strain at the optic nerve head and lead to apoptosis of he ganglion cells; process depend on biomechanical properties of sclera and lamina cribrosa. Our study sustains these findings: computed "R square" is 0.01 for IOPg considered alone as RNFL predictor and triple, 0.03, for IOPg+CH as associated predictors for RNFL loss.

Multiple stepwise regression revealed that RNFL thickness (fiber avg) is much better predicted by age, or associations age + IOPc, age+ CH, Age+ φ (R square is 0.11) than by IOP g, or IOPc, IOPc+ CH (R square is 0.01 respectively 0.03), thus the older definition of glaucoma - that elevated intraocular pressure (IOP) would cause a certain type of damage to the optic nerve - is no longer sustained. As we can see in Table 2, for IOPg considered alone, R square is only 0.013, thus it can explain only 1% RNFL variability, while association age+CH+IOPg account 11% of RNFL variability (ten times more).

Statistics in other studies show also a higher correlation for (in order) superior, inferior quadrants and average thickness of RNFL with IOP [5], [14], [15]. Present work (with a studied sample far greater than other studies) shows also significant statistical correlations between IOP and RNFL thickness, as follows: average, inferior, superior, nasal and temporal (ordered decreasing by relevance). Considering these we improved our daily medical practice, with an appropriate technical and engineering support; uncovering the measure of correlation between IOP and RNFL loss, we also search for other possible RNFL loss causative factors, just as mentioned in other studies [16].

VI. Conclusions

Glaucoma risk or its clinical diagnosis in a patient requires a lot of work and attention between his clinical and paraclinical measured data. Technical support to integrate, compute and judge all patient's collected data offer a better approach of clinical cases.

RNFL thickness is one of the most important parameter used to categorize a patient as healthy, borderline (glaucoma risk) or ill (glaucomatous) and is known to be influenced by elevated IOP in the presence of certain properties of the cornea [13],[14]. Different considered associations between the mentioned parameters - as predictors for RNFL loss - increases the accuracy in categorize a patient. Present work sustain these, showing a good statistical correlation between

RNFL and ORA measured parameters (IOP, corneal properties), as well as with computed corneal specific damping capacity (φ).

The best correlations we found are between age and RNFL thickness (in order: medium, superior, inferior, temporal, nasal, with "r" respectively -0.32, -0.31, -0.24, -0.19,- 0.18 , for all $p< 0.001$); correlations between RNFL thickness (medium and inferior) with IOPc, CH and φ ($r = -0.15$ /-0.16, $p<0.001$) are better than between RNFL (superior and nasal) and IOPc, CH and φ ($r =-0.14/-0.10$, $p<0.001$); there is a very low positive correlation between RNFL (medium, inferior, superior, temporal) and CRF ($r=0.06 / 0.02$, $p<0.001$).

The best predictors for RNFL damage are associations: age + IOPc, age+ CH, Age+ φ (R square is 0.11), but they still only justify a rate of 11% for RNFL variability (loss).

Though, low/medium values of the correlation coefficients (Pearson' r and Spearman not greater than 0.33) show that the studied parameters are not enough for a complete and complex assessment of a glaucoma suspect patient; RNFL thickness decrease is certainly demonstrated now, determined by a more complex combination of factors than IOP and corneal properties [16].

The best predictors for RNFL loss (measure for the optic nerve *structure)* are associations: age + IOPc, age+ CH, Age+ φ, age+CH+IOPg (R square is 0.11), but they still only justify a rate of 11% for RNFL variability (loss).

Future studies with additional collected data about patients (for example: visual field as a measure for the optic nerve *function,* or ocular blood perfusion pressure responsible for optic nerve *nutrition*) are needed to improve rate of prediction for RNFL loss in glaucoma suspects.

Machine Learning Classifiers are also in our focus to increase the speed and accuracy of framing a glaucoma suspect patient, in daily clinical ophthalmological practice.

Conflict of Interest

The authors declare that they have no conflict of interest.

Statement of human rights

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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