Use of Machine Learning on Contact Lens Sensor–Derived Parameters for the Diagnosis of Primary Open-angle Glaucoma

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• PURPOSE: To test the hypothesis that contact lens sensor (CLS)-based 24-hour profiles of ocular volume changes contain information complementary to intraocular pressure (IOP) to discriminate between primary open-angle glaucoma (POAG) and healthy (H) eyes.
• DESIGN: Development and evaluation of a diagnostic test with machine learning.
• METHODS: SUBJECTS: From 435 subjects (193 healthy and 242 POAG), 136 POAG and 136 age-matched healthy subjects were selected. Subjects with contraindications for CLS wear were excluded. PROCEDURE: This is a pooled analysis of data from 24 prospective clinical studies and a registry. All subjects underwent 24-hour CLS recording on 1 eye. Statistical and physiological CLS parameters were derived from the signal recorded. CLS parameters frequently associated with the presence of POAG were identified using a random forest modeling approach. MAIN OUTCOME MEASURES: Area under the receiver operating characteristic curve (ROC AUC) for feature sets including CLS parameters and Start IOP, as well as a feature set with CLS parameters and Start IOP combined.
• RESULTS: The CLS parameters feature set discriminated POAG from H eyes with mean ROC AUCs of 0.611, confidence interval (CI) 0.493–0.722. Larger values of a given CLS parameter were in general associated with a diagnosis of POAG. The Start IOP feature set discriminated between POAG and H eyes with a mean ROC AUC of 0.681, CI 0.603–0.765. The combined feature set was the best indicator of POAG with an ROC AUC of 0.759, CI 0.654–0.855. This ROC AUC was statistically higher than for CLS parameters or Start IOP feature sets alone (both $P < .0001$).
• CONCLUSIONS: CLS recordings contain information complementary to IOP that enable discrimination between H and POAG. The feature set combining CLS parameters and Start IOP provide a better indication of the presence of POAG than each of the feature sets separately. As such, the CLS may be a new biomarker for POAG. (Am J Ophthalmol 2018;194:46–53. © 2018 Elsevier Inc. All rights reserved.)

GLAUCOMA IS A GROUP OF OPTIC NEUROPATHIES characterized by optic nerve changes and visual loss that may progress to blindness if the condition is not diagnosed and treated effectively. Intraocular pressure (IOP) is the most important modifiable risk factor for the onset and progression of glaucoma,[1,2] but the role of IOP in the disease is not fully understood. Many individuals, despite having elevated IOP, never progress to glaucoma.[1] Therefore, while IOP has some ability to discriminate between glaucomatous and healthy eyes, this ability is limited.[3,4] Individual susceptibility to IOP may explain why a significant number of patients with normal IOP can develop glaucoma or experience worsening of glaucomatous damage, while others with elevated IOP show no sign of the disease or little progression. The relationship between glaucomatous damage and IOP is therefore of interest.

Lately, it has been suggested that biomechanical phenomena drive the glaucomatous process leading to typical glaucoma alterations of the optic nerve head (ONH) in susceptible eyes.[5] Elevated IOP exerts forces that are transmitted to the scleral canal and ONH. These forces may expand the scleral canal and deform or displace the lamina cribrosa, depending on the individual eye tissue characteristics and biomechanics. Furthermore, even at normal IOP values, the ocular tissues seem to be subject to substantial levels of IOP-related stress that may be related, at least in part, to its variability. In other words, a given level of IOP-related stress may be physiologic or pathophysiologic, depending on the individual eye.

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Jul 11, 2018.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.07.005

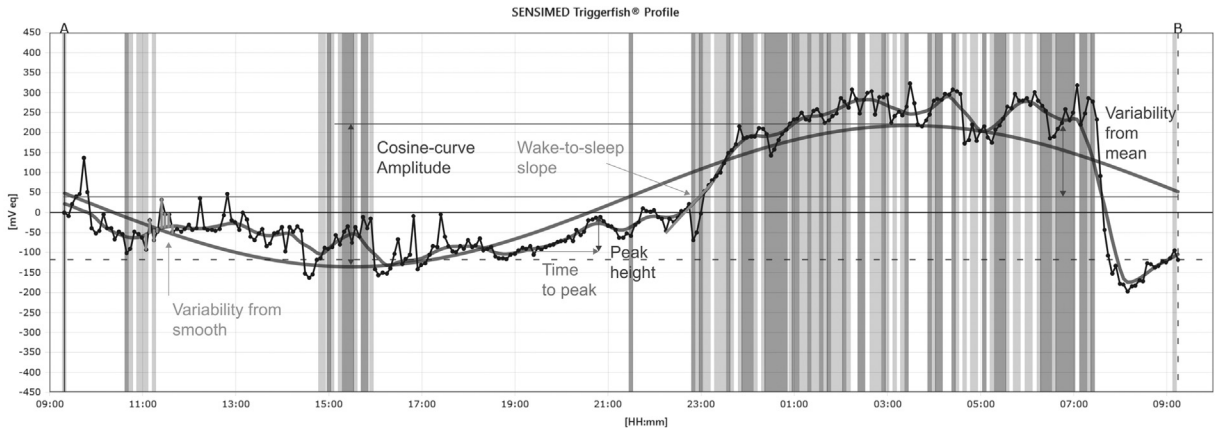

FIGURE 1. Statistical and physiological parameters derived from the Contact Lens Sensor output recorded over 24 hours.

A device based on a contact lens sensor (CLS) that records 24-hour profiles of IOP-related ocular volume changes has become available in the past few years.[6] The device detects ocular phenomena having their origin inside the eye through measurements on the outer surface of the ocular shell. Therefore, the device signal can be expected to be influenced by the eye's biomechanical properties.[7] Certain parameters extracted from the 24-hour CLS profiles have been associated with the visual field (VF) progression rate recorded in treated glaucoma patients.[6] The combination of CLS parameters showed a stronger association with the VF progression rate than the mean, peak, and fluctuation of Goldmann IOP measurements in the same period. This provides support for the hypothesis that CLS parameters could provide information regarding IOP-driven stress and strain. CLS measurements of changes in limbal strain in the face-down position in patients with glaucoma showed a sustained strain increase, especially in patients with past VF worsening.[8] In this study with a total CLS recording duration of approximately 3 hours, patients with glaucoma showed an increase in their mean CLS values when moving to and from face-down position, while age-matched controls did not. Other studies showed differences between 24-hour CLS profiles from healthy and glaucomatous individuals.[9–11] However, these studies were conducted in relatively small cohorts and differed in how CLS profiles were analyzed.

We undertook the current pooled analysis to test the hypothesis that CLS profiles contain information complementary to IOP for the discrimination of primary open-angle glaucoma (POAG) from healthy (H) eyes.

METHODS

THE ANALYSIS WAS PERFORMED ON A DATABASE CONTAINing pooled data from 24 prospective clinical studies and a registry, which were approved by the respective competent body in each center (listed in Appendix 1; Supplemental Material available at AJO.com) and which followed the tenets of the Declaration of Helsinki. The Registry and all but 7 studies (3 investigator driven studies and 4 studies that were part of a cohort study) were registered at ClinicalTrials.gov (trial registration nos. NCT01263535, NCT01217853, NCT01351779, NCT01319617, NCT01347229, NCT01390779, NCT01769521, NCT01507584, NCT01560975, NCT01495312, NCT01561001, NCT01766947, NCT01767753, NCT01828255, NCT01906502, NTC02030886, NCT01912599). Written informed consent was obtained from all participants.

• **SUBJECTS:** Data from 435 subjects (193 healthy and 242 glaucoma) were initially available. To avoid age-related bias, subjects were age-matched using the nearest neighbor method with R – MatchIt.[12] This led to 136 subjects in each group. POAG subjects with a glaucomatous optic disc on clinical examination and glaucomatous VF defects were included. Glaucomatous optic disc features included diffuse or localized neuroretinal rim loss, excavation, and retinal nerve fiber layer defects. Glaucomatous VF features included a pattern standard deviation outside of the 95% normal confidence limits, and/or a Glaucoma Hemifield Test result outside normal limits. For subjects with bilateral glaucoma, only 1 eye was included, either randomly or at the responsible clinician's discretion. H subjects had a normal optic disc and VF. All subjects had open angles on gonioscopy. Subjects with contraindications for CLS wear, including corneal abnormalities, severe dry eye syndrome, and ongoing ocular inflammation or infection, were excluded. POAG patients were treated or not with IOP-lowering medication, as judged appropriate by their treating physician, at the time of CLS recording. Patients who were treated with IOP-lowering drops were instructed to instill these as usual during the recording.

• **CONTACT LENS SENSOR RECORDING:** All subjects underwent a 24-hour recording session with the CLS on 1

TABLE 1. Detailed List and Description of Contact Lens Sensor Parameters Used as Input for the Machine Learning Classification Algorithm

CLS Parameters	Definition
Drop in smoothed OPA curve overnight	How the amplitude of the ocular pulse decreases during the main sleep period. The amplitude over time is modeled with a second-order polynomial and the drop is determined as the start value of the polynomial subtracted from the end value.
Drift	Difference of CLS measurements at the end compared to the start of the recording session, more precisely the difference between the median of the 3 first and 3 last measurements.
Level 7 hours after sleep onset	How high the CLS signal is during the hour that occurs from 7 hours to 8 hours after the main sleep period started. It is calculated as the median of the measurements recorded throughout this hour minus the CLS signal value at the start of the sleep period.
Mean burst amplitude on day 2	Mean amplitude within the 30-second intervals on the second day of the recording. Calculated as the mean of the within-burst amplitudes on the second day of the CLS recording session.
Variability from the mean during sleep	Amount of fluctuation of the CLS signal during the main sleep period. Calculated as $\frac{1}{n-1}\sum_{i=1}^{n}\lvert CLS_{Oi} - CLS_M\rvert$ where n is the number of CLS measurements over the recording period; CLS_{Oi} is the observed CLS signal; and CLS_M is the mean of CLS signals over the recording period.
Amplitude of the CLS recording	Range of measurement values during the recording, calculated as the maximum measurement minus the minimum measurement.
Overnight OPA variability	Standard deviation of the difference between modeled OPA with a second-order polynomial and the raw OPA values.
Drop in OPA overnight	How the amplitude of the ocular pulse decreases during the main sleep period. Determined as the start value subtracted from the end value
Mean burst OPF	Mean over 24 hours of each within-burst ocular pulse frequency during the CLS recording session.
Level 3 hours before sleep onset	How high the CLS signal is during the hour that occurs from 4 hours to 3 hours before the main sleep period started. It is calculated as the median of the measurements recorded throughout this hour.
Level before sleep onset	How high the CLS signal is during the hour that occurs before the main sleep period. It is calculated as the median of the measurements recorded throughout this hour minus the CLS signal value at start of sleep.

CLS = contact lens sensor; OPA = ocular pulse amplitude; OPF = ocular pulse frequency.

Two types of CLS parameters are referred to:

- Measurement: the median of all individual data points in a 30-second recording interval; 288 of these are expected throughout a 24-hour CLS recording session.
- Burst: the 300 individual data points within a 30-second recording interval.

Whenever parameters were derived for day 1, day 2, and the main sleep period of the recording, these were defined as:

- Day 1: from the start of the CLS recording until the time at which sleep onset was detected.
- Day 2: from the time at which the subject's main sleep period ended until the end of the CLS recording.

Main sleep period: From the time of sleep onset until the time at which sleep ended. If there was more than 1 sleep period detected during the 24-hour CLS recording, the main sleep period was the one with the longest duration.

eye (SENSIMED Triggerfish; Sensimed AG, Lausanne, Switzerland), following an initial IOP measurement using applanation tonometry (*Start IOP*). Changes in ocular dimensions are detected in the limbal area by strain gauges embedded in the CLS and communicated wirelessly to a periorbital antenna connected to a recorder unit with a data cable. Measurements expressed in millivolt equivalents (mV eq) are acquired during 30 seconds (*burst*) repeated every 5 minutes. The technology is described in more detail elsewhere.[13–15]

• **STATISTICAL ANALYSES:** CLS parameters were computed from recordings with a minimum duration of 22 of the 24 hours and at least 230 valid measurements of the 288 expected values. Bursts were considered valid if at least 30 of the 300 data points were available for the 30-second data acquisition period. We only included recordings that were not affected by jumps (sudden and permanent changes in CLS signal of at least 120 mV eq between 2 consecutive Triggerfish medians, for example owing to eye rubbing provoking CLS movement) and for

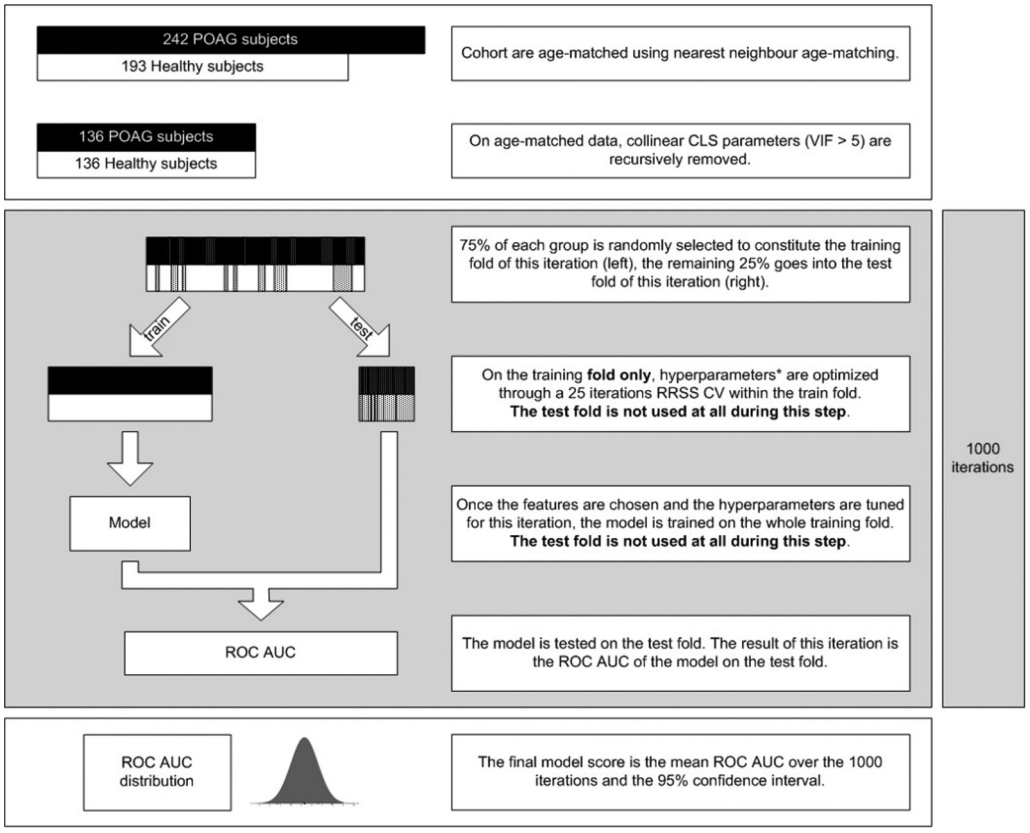

FIGURE 2. Steps of the repeated random subsampling cross-validation process used to build the models and evaluate the statistical validity of the average performance. *Define internal parameters of the model. Hyperparameter optimization is done within a 25-iteration repeated random subsampling cross-validation. In the case of the random forest model, the optimized hyperparameter is the number of decision trees. In the case of the simple decision tree, no hyperparameter is optimized and this step is skipped. CLS = contact lens sensor; POAG = primary open-angle glaucoma; ROC AUC = area under the receiver operating characteristic curve; RRSS CV = repeated random subsampling cross-validation; VIF = variance inflation factor.

which CLS parameters required for analyses could be computed.

Contact Lens Sensor Parameters. For each subject, statistical and physiological CLS parameters were derived from the recorded signals (Figure 1). Some of the parameters were statistics-related, such as the mean, standard deviation (SD), minimum, maximum, and amplitude of the CLS signal medians across all bursts. Other parameters were derived from data points within bursts. For these, we extracted intra-burst amplitude and SD, as well as ocular pulse amplitude (OPA) and frequency (OPF), for each burst of the recording and calculated the same statistics as described above.

Moreover, we extracted the same preceding parameters, but only on the bursts of the first and second day of the overnight recording session, as well as on those of the subject's main sleep period. Sleep was asserted from the data by a computerized detection of eye blinks on the CLS curves and considering sleep as the period without eye blinks. In addition, we defined parameters from the CLS signal level measured each hour up to 7 hours after the start and before the end of the main sleep period, as well as each hour up to 7 hours before the main sleep period start. We also computed the CLS signal difference between the end and the start of the recording session, respectively, and the slope of the CLS signal at sleep onset and at awakening. The list and definitions of the main CLS parameters are provided in Table 1.

Multicollinearity Reduction. CLS parameters are intrinsically correlated to one another, which could potentially lead to undesired effects of multicollinearity in the analyses. To minimize these effects, we used the Variance Inflation Factor (VIF), which qualifies the level of collinearity between parameters. Highly collinear CLS parameters (VIF $\geq$ 5) were discarded. The cutoff of 5 was chosen to avoid losing significant information.[16]

Discrimination Between Primary Open-angle Glaucoma and Healthy Eyes. Machine learning (ML) models were developed to classify POAG and H eyes (*classes*) based on Start

TABLE 2. Classification of Primary Open-angle Glaucoma and Healthy Eyes Using the 3 Feature Sets

Feature Set	N		AUC	SD	CI_{Low}	CI_{High}
	POAG	H				
1. CLS parameters	136	136	0.611	0.057	0.493	0.722
2. Start IOP	136	136	0.681	0.040	0.603	0.765
3. CLS parameters + Start IOP	136	136	0.759	0.050	0.654	0.855

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CLS = contact lens sensor; H = healthy; IOP = intraocular pressure; N = number of subjects; POAG = primary open-angle glaucoma; SD = standard deviation.

IOP, CLS parameters, and both feature sets combined. During the phase called *training*, a model was built using a subset of the available subjects whose classification outcome is known (*training fold*). During the second phase, called *test*, another subset of the available subjects, also with known classification outcomes (*test fold*), was used to attest for the classification performance of the built model. To do that, a performance score had to be chosen. Area under the receiver operating characteristic curve (ROC AUC) was used as performance score, as it is a common metric used by both ML and medical communities in binary statistics associated with diagnostic tests. Several ML classification algorithms are available for such analyses. The random forest (RF) algorithm was chosen for its simplicity of use and capacity to help interpreting the results as well as determining the best discriminative features. Provided in the Python ML framework Scikit-learn, the RF algorithm operates by constructing decision trees (DT) during the training phase and outputting the class that is the most often returned by the individual decision trees during the test phase.[17] A DT is a classification algorithm that creates a discriminative model by learning simple decision rules inferred from the features. Since there is only 1 feature to analyze in the models built using Start IOP only, a simple DT with 2 branches and a depth equal to 1 was used.

We thereby generated, validated, and compared 3 different feature sets to discriminate between POAG and H eyes. A process was developed and applied to build the models and evaluate the statistical validity of the average model performance. This process was based on a repeated random subsampling cross-validation (RRSS CV). Our RRSS CV consists in randomly splitting the subjects into 1000 training and test folds, select the best discriminative features for each training fold, and then averaging the ROC AUCs obtained on the corresponding 1000 test folds to give a final estimation of the average performance of the ML models for the discrimination between POAG and H eyes. RRSS CV has the advantage that the number of subjects in each training and test fold does not depend on the number of iterations. However, it has the drawback that some subjects may never be part of the test fold, whereas others can be included more than once. Nevertheless, each train and test fold will have a unique composition of POAG and H subjects. The process is described in Figure 2. ROC AUC values for different feature sets and distributions of feature values in H and POAG eyes were compared using 2-tailed *t* tests, with $P < .05$ being considered as statistically significant.

RESULTS

THE DATA OF 272 AGE-MATCHED SUBJECTS (136 H AND 136 POAG) meeting the inclusion and exclusion criteria were analyzed. Mean (SD) age was 58.5 (12.1) years for POAG and 56.1 (12.6) years for H ($P = .12$; 2-tailed *t* test). We evaluated 3 feature sets for discrimination between POAG and H eyes: (1) CLS parameters; (2) Start IOP; (3) CLS parameters and Start IOP combined.

The distributions of ROC AUCs obtained over 1000 iterations in the test fold for each of the feature sets are presented in Table 2. The mean ROC AUCs for the models built using CLS parameters or Start IOP alone are statistically different ($P < .0001$) and just above the informative limit (0.611 and 0.681, respectively). However, the 95% confidence interval for the mean ROC AUC using the CLS parameters includes 0.5, equivalent to a random classifier and therefore indicating that CLS parameters alone are borderline to discriminate between POAG and healthy eyes. When the CLS parameters and Start IOP are combined, a synergistic effect is apparent, with the resulting mean ROC AUC being significantly higher than for each of the Start IOP and the CLS feature sets individually (both $P < .0001$).

The most important features selected by the RF algorithm in each of the feature sets were ranked according to their average weight over the 1000 iterations of RRSS CV (Table 3). With only slight variations to their internal ranks, the same CLS parameters ranked highest in both the CLS parameters and the combined feature sets (ie, contributed most of the information contained in the CLS recordings). All but 1 feature showed a significant difference between H and POAG eyes. In general, larger values were associated with a diagnosis of POAG.

DISCUSSION

CLINICAL DECISION MAKING IN GLAUCOMA MANAGEMENT involves taking account of a wide variety of variables, including an individual's age, family history, optic disc and VF characteristics, IOP level, and other risk factors. The contribution of different glaucoma risk factors has

TABLE 3. Summary of Most Important Features Discriminating Primary Open-angle Glaucoma From Healthy Eyes Ranked in Each of the Feature Sets

Features	Rank in CLS	Rank in Start IOP	Rank in CLS + IOP	Diagnosis	Mean (SD)	*P* Value	Relationship With Diagnosis
Drop in smoothed OPA curve overnight (mV eq)	1	NA	2	POAG	−0.005 (0.032)	.009	Larger value associated with POAG
				H	−0.014 (0.022)		
Drift (mV eq)	2	NA	3	POAG	139 (132)	.005	Larger value associated with POAG
				H	92 (146)		
Level 7 hours after sleep onset (mV eq)	3	NA	4	POAG	111 (111)	.002	Larger value associated with POAG
				H	69 (104)		
Mean burst amplitude on day 2 (mV eq)	4	NA	5	POAG	2.941 (0.667)	.002	Larger value associated with H
				H	3.189 (0.660)		
Variability from the mean during sleep (mV eq)	5	NA	6	POAG	43 (19)	.003	Larger value associated with POAG
				H	37 (14)		
Amplitude of the CLS recording (mV eq)	6	NA	7	POAG	440 (96)	.010	Larger value associated with POAG
				H	409 (102)		
Overnight OPA variability (mV eq)	7	NA	9	POAG	0.016 (0.006)	.032	Larger value associated with POAG
				H	0.015 (0.006)		
Drop in OPA curve overnight (mV eq)	8	NA	8	POAG	−0.015 (0.043)	.010	Larger value associated with POAG
				H	−0.029 (0.040)		
Mean burst OPF (Hz)	9	NA	12	POAG	63 (8)	.146	Larger value associated with H
				H	64 (9)		
Level 3 hours after sleep onset (mV eq)	10	NA	11	POAG	−61 (83)	.011	Larger value associated with POAG
				H	−88 (91)		
Level before sleep onset (mV eq)	11	NA	10	POAG	−11 (48)	.044	Larger value associated with POAG
				H	−22 (41)		
Start IOP (mm Hg)	NA	1	1	POAG	18 (5)	<.0001	Larger value associated with POAG
				H	14 (3)		

CLS = contact lens sensor; H = healthy; IOP = intraocular pressure; mV eq = millivolt equivalent; NA = not applicable; OPA = ocular pulse amplitude; OPF = ocular pulse frequency; POAG = primary open-angle glaucoma; SD = standard deviation.

been extensively studied at a population level. However, the ability to predict the risk of an apparently healthy eye developing glaucoma or the risk of an eye with glaucoma deteriorating over time remains relatively limited. IOP remains the major modifiable risk factor for glaucoma onset and progression, but the level of IOP at which glaucoma onset or progression occurs varies widely among individuals. To enhance glaucoma management, therefore, it should be an important goal to identify additional risk factors.

In the current study, 136 POAG patients and age-matched controls were used to evaluate 3 feature sets for discrimination between POAG and H eyes: CLS, Start IOP, and CLS Parameters + Start IOP combined. When the CLS parameters and Start IOP are combined, there was an apparent synergistic effect, with the resulting mean ROC AUC being significantly higher than for each of the Start IOP and the CLS feature sets individually (both $P < .0001$). Thus, the use of CLS parameters in addition to the Start IOP significantly increased the average performance of algorithms to discriminate POAG and H eyes.

It should be noted that POAG patients in the current study were treated at the discretion of the physician. A majority of them were on IOP-lowering medications. This is likely to have caused the IOP distribution of POAG and H subjects to be more similar than would be expected for untreated patients, and thus made the task of discriminating the groups based on IOP, and IOP-related variables such as CLS parameters, more difficult. This may explain the relatively low AUC values obtained in the current analysis.

Among the relevant CLS parameters discriminating POAG from H subjects, those with larger values were generally associated with a diagnosis of POAG (Table 3). In other words, CLS recordings in individuals with POAG tended to show more variability than recordings in H subjects, resulting in larger average amplitudes of the studied parameters in POAG patients. Moreover, signal levels preceding and during sleep were higher in POAG patients. These findings are similar to a previous report where 24-hour CLS recordings were modeled for groups of healthy and POAG subjects.[9] In this report, the amplitude of the cosinor function that was fitted to CLS data was larger and the nocturnal values were also higher in the POAG patients than in the healthy ones. It is, however, not known whether the CLS signal has a larger amplitude because of differences in IOP between H and POAG or differences in scleral biomechanical properties. Evidence suggests that the scleral location that is most influential on ONH biomechanics is

the peripapillary sclera, while the CLS readings are mostly influenced by the limbal sclera.[18] At present, it is not known to what degree scleral properties at these 2 locations are correlated. Results from this study seem to suggest that many factors other than IOP are involved in glaucoma development. This theory is reflected by CLS measurements, which are composed of changes in IOP, intraocular volume, and the biomechanical properties of the eye.

To investigate whether CLS profiles contained valuable information related to glaucoma, and in line with our hypothesis that CLS detects how ocular tissues respond to IOP-related stresses, a data-driven methodology based on a repeated random subsampling was preferred to usual analysis methods involving univariate and/or multivariate analyses. This choice was guided by our interest to achieve data mining analyses, as opposed to elaborate single specific classification models, with assurance that overfitted results would be avoided. Nevertheless, the performance score used with our methodology (ROC AUC) reflects the sensitivity/specificity commonly found in prior publications.

We applied ML algorithms to extract the best CLS parameters. Several ML classification algorithms exist. Some, such as *support vector machines* or *artificial neural networks*, function rather as "black boxes" lacking the ability to identify the best discriminative parameters explicitly. For the current analysis, the RF algorithm was selected because of its inherent simplicity and capacity to facilitate interpretation of results, as well as to determine the best discriminative features.

For each of the CLS parameters that was most frequently selected by the RF algorithm, as well as for the Start IOP (in our data), a single statistical test was used to compute the *P* values to compare the distribution of each parameter between H and POAG. These *P* values were not used to select the best features, but just to confirm them at the end of the analysis. Thus, correction of *P* values for multiple simultaneous comparisons was not relevant to the current study.

The RRSS CV process used to build our models and measure their performance has the advantage that the number of samples in each training and test fold does not depend on the number of iterations (unlike, for example, what occurs in a standard K-fold CV). This design means that some subjects may never be part of the test fold, whereas others can be included more than once. It is unlikely this had any significant effect on the validity of our results, as the number of iterations (1000) was high.

In the current study, the 24-hour CLS profile contained information contributing to the discrimination between H and POAG. We speculate that tissue properties that differ between POAG and H eyes contribute to this finding. It has been suggested that biomechanical phenomena drive the glaucomatous process, leading to typical glaucoma alterations of the ONH in susceptible eyes.[5] Further, decreased scleral rigidity was associated with more deformation of the lamina cribrosa, suggesting more optic nerve damage when IOP is elevated.[18,19] However, there is no readily available method to measure such tissue properties in living eyes, which therefore is unknown for the subjects analyzed here. Hence there is no means to further explore this hypothesis. Nevertheless, the CLS's unique ability to provide information on the eye's behavior, in addition to IOP, could therefore be both clinically relevant and valuable.

In summary, a pooled analysis of data from 24 prospective clinical studies and a registry was performed to test the hypothesis that CLS-based 24-hour profiles of ocular volume changes contain information complementary to IOP to discriminate between POAG and H eyes. The feature set combining CLS parameters and Start IOP provide a better indication of the presence of POAG than each of the feature sets. Thus, CLS parameters may be additional and novel risk factors for predicting the onset and progression of POAG.

FUNDING/SUPPORT: SENSIMED AG, LAUSANNE, SWITZERLAND, PROVIDED FINANCIAL SUPPORT FOR THIS RESEARCH AND participated in the design of the research, data management, data analysis, interpretation of the data, and preparation, review and approval of the manuscript. The University of Applied Sciences Western Switzerland (HES-SO) participated in the data analysis and data interpretation, as well as preparation, review, and approval of the manuscript in the framework of this research project, partially funded by the Swiss Commission for Technology and Innovation (CTI) under grant 17325.1 PFLS-LS. Financial Disclosures: Keith R. Martin: Allergan (consultant [C]), Santen (C), Bausch & Lomb (C), Novartis (C), Quethera (C, financial interest, patent), Sensimed (C), VISUfarma (C). Kaweh Mansouri: Santen (C), Sensimed (C), Topcon (grant support [S]), Alcon (S), Implandata (C), Allergan (S), Optovue (S), New World Medical (C). Robert N. Weinreb: Aerie Pharmaceutical (C), Alcon (C), Allergan (C), Bausch & Lomb (C), Eyenovia (C), Novartis (C), Sensimed (C), Unity (C), Heidelberg Engineering (S), Optovue (S), Topcon (S), Zeiss Meditec (S). The following authors have no financial disclosures: Robert Wasilewicz, Christophe Gisler, Jean Hennebert, and Dominique Genoud. All authors attest that they meet the current ICMJE criteria for authorship.

A list of Research Consortium members is available as Appendix 2 (Supplemental Material available at AJO.com).

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