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Glaucoma Diagnosis: from the Artisanal to the Defined

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Précis:

In 400BC, Hippocrates wrote the first record of glaucoma. Since then, increasingly objective diagnostic techniques have enabled earlier detection of glaucoma and its progression, providing greater certainty in decision-making and early medical and surgical intervention.

Glaucoma is a chronic, irreversible optic neuropathy, frequently with a surreptitious course; it is the second leading cause of blindness globally. Advances in functional and structural measures of disease progression are transforming glaucoma diagnosis from an art to a science: applanation tonometers have supplanted finger tension intraocular pressure (IOP) measurement, OCT and other imaging modalities have enabled *in vivo* objective, quantitative assessments of neural tissue loss, and rigorous statistical algorithms have replaced subjective visual assessments of perimetric and imaging results. These innovations have enabled earlier detection of glaucoma progression than ever before, contributing to more judicious use of the array of medical and surgical treatments that have evolved in parallel to diagnostic advances. The aim of this paper is to review the history of glaucoma diagnosis, covering more than 2000 years of innovation.

Early History of Glaucoma

Hippocrates' *Aphorisms*, published in 400 BC, included the first known record of glaucoma. He referred to the entity as "glaucosis", a condition associated with dimness of vision and eventual blindness that was observed among the infirmities of age. (1) In his text *De Generatione Animalium*, Aristotle (384-322 BC) postulated that, in the same way that a shallow body of water exhibited a light, bright color and a deeper one appeared dark, the color of the eye depended on the amount of water within it. (2) Centuries later, Galen (129-216 AD) defined glaucoma as a condition in which the pupils became discolored due to changes in the fluids within the eye. (3) Aetius (482 – 565 AD) described two distinct

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categories of glaucoma: a curable defect of the lens and an incurable abnormality of the pupil. (4)

As Jacques Daviel began to describe the process of lens extraction for treatment of advanced cataracts in the 1750s, it became clear that cataracts and glaucoma were distinct entities. (4) In the 18th century, the majority of eyes diagnosed with glaucoma had advanced disease, characterized by a dilated, poorly reactive pupil and lens opacity that resulted in the observation of a greenish reflection. The contemporary ophthalmologic literature listed this as a prominent sign of glaucoma. (4)

In his 1826 *Nouveau traité des maladies des yeux*, St. Yves described this reflection and other clinical features of advanced glaucoma. (4) William Mackenzie soon thereafter delineated six major stages of the disease: a greenish reflex of the pupil marked the first stage, hardness of the eyeball occurred in the second stage, and by stage six, the cornea had ulcerated and the eye had atrophied, the perceived final consequence of advanced glaucoma. Mackenzie also suggested a posterior sclerotomy as a means of relieving pathologic hardness of the eyeball. (5)

Historical Notions of Fluid and Pressure in the Eye

Banister first suggested the possible relevance of eye pressure to glaucoma in 1626 when he described an association between the resistance of the eyeball to indentation by the physician's finger and ocular disease. (4) It wasn't until the 19th century that the cause of this resistance to indentation became clear. In 1860, Schwalbe injected dye into the anterior chamber and noted that it subsequently appeared in the veins on the surface of the globe, leading him to the conclusion that the anterior chamber was a lymphatic space in communication with the anterior ciliary veins. (4) In 1870, Theodor Leber described the aqueous outflow pathway, filtration through the trabecular meshwork, and flow through ciliary and vortex veins. (4) His work suggested that, with the exception of early fetal life, the rate of outflow was always proportional to the perfusion pressure. (4) Leber's filtration theory stated that, to maintain a stable *in vivo* pressure, consistent formation of fluid must match and thus compensate for the steady loss of fluid via the outflow pathway. (4) Eric Seidel refined Leber's filtration theory in 1920 to account for the effects of the colloid osmotic pressure of the plasma proteins and the active transfer processes in the formation of aqueous. (4)

In the 1870s, Priestley Smith stated that the glaucomatous damage at the optic nerve head (ONH), known by that time as cupping, was a manifestation of not only mechanical forces but also a combination of vascular and metabolic changes in the eye. Further, he suggested that these forces must be present chronically in order to alter the nerve in a detectable way. (6) Smith also proposed that narrowing of the circumferential space with age could predispose to glaucoma. (7) This narrowing was reliant upon the anatomic principle that, in states of hyperemia, the ciliary processes are pushed forward, pressing the iris against the anterior angle wall. (7) In a seminal animal study that contributed to this theory, Smith demonstrated that a small increase in vitreous chamber pressure caused sufficient anterior movement of the lens and suspensory ligament to close the angle of the anterior chamber. (6) This work

underscored the importance of individual angle anatomy in determining glaucoma risk, prompting Trantas in 1907 (and later, Salzmann, Koeppe, Troncoso, and Barkan) to promote gonioscopy as a routine diagnostic technique. (4)

Given the mounting evidence that intraocular fluid dynamics contributed to glaucoma damage to the optic nerve, it was perhaps unsurprising that around the same time as Smith's work, more precise methods for assessing IOP began to replace finger tension IOP assessment. Weber invented the first applanation tonometer in 1867, which was followed by versions by Donders (first scleral indentation tonometer, 1868), Maklakoff (1892), and Hjalmar Schiøtz (1905). (4) In 1950, Hans Goldmann introduced the Goldmann tonometer, one of his many contributions to more precise measurement of the eye and its function. (4)

Glaucoma and the Visual Field

Leonardo da Vinci (1452 – 1519) noted that the cornea and aqueous humor bend light rays and described how the temporal visual field (VF) extended 90 degrees from fixation. (8) In 1668, Mariotte described the blind spot and connected it to the location of the optic disc (9) Thomas Young's work in 1807 generated a more precise characterization of the VF, extending 50° superiorly, 70° inferiorly, 60° nasally, and 90° temporally. (10)

In 1856, von Graefe proposed the incorporation of VF assessment into clinical practice. (8) His campimeter consisted of a sheet of paper with radial rows of dots that served as stimuli. With this tool, he plotted paracentral defects, though initially the blind spot rather than the fixation point was recorded as zero. (8) In the 1940s, Goldmann's invention of a hemispherical bowl perimeter for static and kinetic perimetry fostered significant progress in VF testing. (8)

Optic Nerve: Structure and Relevance to Glaucoma

In the second century AD, Galen drew the optic nerve as a hollow structure; the notion of a hollow nerve persisted for more than 1000 years. (11) Anthoni van Leeuwenhoek is credited with the first illustration of a peripheral nerve in 1673, in which he portrayed a bundle of myelinated axons as a channel that collapsed following the escape of fluid humor. (11) In his 1755 atlas, *Descriptio anatomica oculi humani*, Johann Gottfried Zinn depicted the optic nerve as a solid structure, countering the theory of the hollow optic nerve. (11)

The invention of the ophthalmoscope by physicist Hermann von Helmholtz in 1851 revolutionized ophthalmology by enabling direct examination of the optic nerve (Figure 1). (12) Helmholtz's creation quickly took on life of its own, and the following decades brought hundreds of iterations of the original model, each attempting to improve upon one of his three essential elements for a functional ophthalmoscope: a light source, a means of reflecting light into the eye, and a method of focusing the image on the fundus. (12) Thomas Edison's did not invent the light bulb until nearly three decades later, so these early models used a variety of light sources that required a greater degree of maintenance, including a naked candle placed next to the patient's face and, later, lamps that burned oil, paraffin, and gas. (12) In recognition of the ophthalmoscope's role in accelerating the understanding and diagnosis of eye diseases, Albrecht von Graefe presented Helmholtz with a cup at the 1858

Heidelberg Ophthalmological Congress inscribed with the message, “To the creator of a new science, to the benefactor of mankind, in thankful remembrance of the invention of the ophthalmoscope.” (13)

Efforts to understand many ophthalmologic diseases accelerated following the invention of the ophthalmoscope, and glaucoma was no exception. In 1851, utilizing an ophthalmoscope to examine the optic nerve in a glaucomatous eye, Heinrich Mueller became the first ophthalmologist to observe and describe the depression of the optic disc, which he attributed to increased vitreous pressure acting upon the lamina and forcing it to recede. (4) In 1854, Eduard Jaeger documented a similarly altered optic disc based on his observations with a monocular indirect ophthalmoscope, though he interpreted the changes as swelling of the disc relative to the surrounding retina (Figure 2). (4, 11) In 1855, Weber first described the optic disc as “cupped” in patients with glaucoma, consistent with Mueller’s notion that the disc was depressed rather than swollen or bulging. (14) These findings confirmed the relevance of optic nerve changes to glaucoma and provided early evidence of a structure-function correlation in the disease.

Assessment of the Optic Nerve: Toward Objective Measures

Despite the development of a multitude of proposed rating scales and methods of standardization, optic disc assessment was fraught with subjectivity and imprecision. In 1976, Paul R. Lichter published a study that delineated the limitations of optic disc evaluation, underscoring the extent of disagreement among observers, and even among repeated evaluations of the same fundus photograph by the same observer. (15)

Distinguishing the physiologic from the pathologic in terms of disc cupping proved a difficult task, even for experts in glaucoma. Nonetheless, a growing body of research continued to assert the importance of this type of structural evaluation for understanding the state of a patient’s disease. Airaksinen and colleagues contributed to this understanding of the importance of the neuroretinal rim area in a series of papers published in 1985, establishing that neuroretinal rim area was significantly reduced in patients with glaucoma relative to healthy controls. (16) They found that this reduction in area correlated with loss of retinal nerve fibers, both diffusely and in localized areas. (17) The group’s work revealed the functional implication of this structural change: there was a statistically significant correlation between neuroretinal rim area and visual VF loss, particularly in terms of overall retinal sensitivity, but also for localized VF changes. (18) This work provided an additional factor beyond cupping to consider when assessing the ONH, but the assessments remained highly operator-dependent.

Around the same time, the invention of the Rodenstock Optic Nerve Head Analyzer nudged glaucoma diagnosis toward more objective measures. This tool, a video-ophthalmograph, captured multiple stereoscopic images, culminating in a topographic representation of the optic disc. With the help of a microcomputer, the device generated data for a number of standard parameters of optic disc evaluation: vertical cup-disc ratio, vertical optic disc diameter, cup volume, and neuroretinal rim area. In contrast to the high degree of variability among optic nerve assessments by experts, this video-ophthalmograph produced more

reproducible and reliable data. In other words, it was significantly more consistent in analyzing the same fundus images multiple times as well as in analyzing multiple fundus images from the same patient in the same sitting. (19) Subsequent studies demonstrated a high degree of correlation between the results of the Rodenstock analyzer and the assessments of experts based upon disc photographs; these studies considered cup-disc ratio, neuroretinal rim area, and optic disc area. The authors attributed the disagreement that did exist to the relative difficulty for humans to account for notching and irregularity within the ONH. (20, 21)

By the mid-1990s, several similar analyzers had come to market, which utilized three main strategies for computer-assisted optic nerve imaging: photographic or video image digitization, grid projection over the ONH, and laser scanning. Generally, these instruments yielded accurate and highly reproducible data for ONH characteristics. However, the high cost of the instruments and uncertain clinical utility (the range of measurements for normal and glaucomatous eyes had significant overlap) limited their early adoption. (22)

The Ancillary Study arm of the Ocular Hypertension Treatment Study (OHTS) assessed another technology for topographically measuring the optic disc: confocal scanning laser ophthalmoscopy (CSLO). This technique was possible owing to the development of the scanning laser ophthalmoscope by Webb in 1980 and the addition of descanning and confocal optics by Van Norren in 1987. (23) The study, which evaluated the likelihood of progression to primary open angle glaucoma (POAG) in patients with ocular hypertension, found that structural abnormalities as measured by CSLO – including Heidelberg retina tomograph (HRT) analysis topographic measurements of the neuroretinal rim and optic cup – could predict which patients would subsequently develop POAG. (24–26) Eyes that progressed to POAG demonstrated a greater rate of change in CSLO ONH parameters than those that did not develop POAG, and these findings held true when the CSLO parameters were considered alone or in combination with other relevant characteristics of the study group, including age, IOP, central corneal thickness, and visual pattern standard deviation. (27–30)

If CSLO and other automated, objective measures were to be included in clinical practice, it would be important to consider the utility of these techniques relative to more subjective functional measures (i.e., conventional perimetry). Chauhan and colleagues found that scanning laser tomography had a greater sensitivity than VF for detecting eyes with glaucoma. Their study of 77 patients revealed that most patients with VF features consistent with glaucoma also had typical disc changes, but the reverse was not true – less than half of patients with disc abnormalities exhibited the characteristic VF features. (31)

A longitudinal study that classified eyes based on patterns of disc damage demonstrated that certain patterns had a greater tendency toward VF progression than others. In particular, as compared to eyes with optic disc changes characterized as myopic or generalized, eyes categorized as senile sclerotic had a greater propensity for subsequent VF worsening. (32)

Nerve Fiber Layer Assessment: Subjective to Objective

In the 1980s, research led by Quigley and colleagues demonstrated that a change in retinal thickness due to RNFL thinning secondary to ganglion cell death was a sensitive indicator of glaucomatous damage that preceded detectable changes in ONH appearance (i.e., cupping) and measurable loss of visual function. (33–35) The glaucomatous RNFL changes occurred in a patterned way – particularly affecting the superior and inferior poles of the optic disc – that was distinct from patterns of atrophy in other ocular diseases including toxic amblyopia, ischemic optic neuropathy, and chronic papilledema. (34) Further, the group’s research revealed a correlation between the pattern of RNFL abnormalities and location of VF defects. (33) Despite the potential importance of RNFL thickness for identifying patients likely to progress to POAG, at the time of this work, precise measurements could only be made on enucleated eyes. (34) In the studies that evaluated eyes *in vivo*, experts used a hand magnifier and fundus photographs to make categorical assessments of the RNFL (normal, local defects, diffuse atrophy). (33) Primate studies by the Quigley group demonstrated that loss of 50% of the RNFL tissue in a given area was required to detect a change on clinical exam, yet a reduction in RNFL thickness of only 10-20 μm could be a harbinger of VF loss. (35) It was evident that more precise measurement techniques would be necessary for RNFL to reach its full potential as a diagnostic marker of diagnosis of glaucoma and detection of its progression.

Further evidence of the importance of RNFL thinning for predicting the onset of VF loss came from Sommer and colleagues, whose work established a temporal relationship between thinning of the RNFL and the onset of VF loss. Early work by this group suggested that RNFL thinning occurred as early as five years prior to changes on Goldmann perimetry. (36) Of note, this research was reliant on subjective assessments by an expert who considered the “apparent thickness of the nerve fiber layer as it crossed the rim of the cup,” determining whether the layer was “elevated”, “flattened”, or “lost”. (37) The group published a large study in 1984 that sought to evaluate the validity of this kind of RNFL assessment. They found that, when two expert observers evaluated the RNFL on red-free photographs with the discs blocked out, the sensitivity and specificity of their evaluation in terms of accurately identifying glaucomatous eyes were 80% and 94%, respectively. Variations occurred by observer and by the age, race, and severity of VF loss of the subjects. (38)

Despite the limitations of a subjective approach to RNFL assessment, this type of evaluation still seemed a worthwhile diagnostic exercise; a longitudinal study published in 1991 demonstrated that RNFL abnormalities were detectable by individual assessment of fundus photographs years in advance of VF defects. Furthermore, while the location of the VF defect generally corresponded with that of the RNFL abnormality, the RNFL loss was generally more widespread, suggesting that the VF loss may subsequently become more extensive. (39)

Using the Rodenstock analyzer to capture optic nerve topography and a method for mapping the contour of the parapapillary nerve fiber layer, Caprioli et al. found peripapillary RNFL thinning in areas of nerve fiber layer loss, cupping, and VF loss. Specifically, there was an

overall reduction of the nerve fiber layer thickness with particularly marked loss in the superior and inferior poles, the usual site of thicker bundles of nerve fibers that converged at the optic disc. This approach to structural evaluation, which incorporated measurements of the peripapillary RNFL, better discriminated between normal and glaucomatous eyes than the conventional measures of cup/disc ratio, disc rim area, and cup volume. (40)

Ellipsometry

In the early 1990s, ellipsometry emerged as an alternative method for measuring RNFL thickness. It relied on the assumption that polarized light that propagated through the retina would be rotated in proportion to the RNFL thickness. (41) As such, ellipsometers, when coupled to laser scanning systems, could utilize data about the polarization state of reflected light to quantitate RNFL thickness. Indeed, early studies in ellipsometry demonstrated a strong correlation between degree of polarization and subsequent histopathological analysis of RNFL thickness. (42)

In ellipsometry, light returning from all depths of the retina was collected, and RNFL thickness was determined from the retardation of the reflected light with three key assumptions. First, that the RNFL was the main source of birefringence in the tissues of the eye. Second, that most of the light was reflected from the outer margin of the retina and thus double-passed the full thickness of the RNFL. And finally, that the birefringence of the RNFL was homogeneous. Later work proved many of these assumptions to be incorrect. For instance, the anterior segment exhibited significant birefringence, and the specific corneal polarization axis varied considerably among individuals. This anterior segment birefringence had a significant effect on the measurement of the RNFL. (43)

Several efforts were made to adjust polarimetry techniques to overcome these sources of error, including methods of individualized compensation for the magnitude and axis of anterior segment birefringence, and these techniques ultimately proved superior to the conventional modes of fixed compensation. (44) A 2007 study by the Advanced Imaging for Glaucoma Study group found that the discriminating ability of even the most sophisticated scanning laser polarimetry device was inferior to optical coherence tomography for detecting glaucoma (Figure 3). (45)

Optical Coherence Tomography in Clinical Practice

Optical coherence tomography (OCT) was developed as a means for non-invasive, objective, accurate, rapid, reproducible, and quantitative tissue sampling, providing an “optical biopsy”. The first OCT images appeared in *Science* in 1991. (46) Though early OCT studies focused on the anterior segment, its greatest utility has been in imaging the structures in the back of the eye. With regard to glaucoma, OCT has led to a deeper understanding of the disease’s effect on the microstructure of the retina and optic nerve. In particular, OCT has enabled a detailed evaluation of a diverse set of structures relevant to glaucoma, including the RNFL, ONH, macular tissues, retinal and optic nerve vasculature, anterior chamber angle, and aqueous outflow system. (47)

OCT has enabled detection of glaucoma damage before measurable VF loss develops. Loss of approximately 17% of RNFL thickness was found to be necessary, on average, to detect VF loss. (48) A longitudinal study recapitulated this finding, demonstrating that OCT detected structural progression approximately one year before initial VF loss or worsening of existing VF loss could be detected. (49)

The understanding soon emerged that, as glaucoma progressed to the tipping point – the point at which VF changes became detectable in addition to OCT abnormalities – and beyond, progression continued in both structure and function until the OCT RNFL thickness reached its measurement floor. At this point, the RNFL thinned to the practical minimal measurable value, after which progression was detectable in function, but not RNFL thickness change. (49)

In addition to RNFL thickness, the macular measurements of ganglion cell complex (GCC) and ganglion cell-inner plexiform layer (GCIPL), as determined by Fourier-domain OCT, outperformed VF in detecting progression in early glaucoma. (49) The utility of macula structure as a maker of glaucoma and its progression was initially suggested by Zeimer and colleagues, who proposed that loss of retinal thickness occurred not only at the optic disc, but also at the perifoveal retina. (50) More recent work has shown that these measurements had the added benefit of exhibiting measurable progression in moderate to advanced cases, past the point at which RNFL thickness reached the measurement floor. (49) However, a similar measurement floor was proposed to exist at a later point for GCC and GCIPL. (51) Recently, data emerged suggesting that, beyond the floor for detecting progression in RNFL, GCC, or GCIPL, OCT-measured ONH parameters continued to progress, providing a structural correlate to the continued VF loss. (52) These ONH parameters, including cup/disc ratio and cup volume, may be useful for detecting progression in advanced glaucoma.

Early detection of presence and progression of glaucoma has been key to optimal management of the disease. Over the last several decades, new technologies like OCT have facilitated progressively earlier and more sensitive detection of progression, and the utility of these tools has been strongest when each data point is considered in the context of what else was known for a given patient. For instance, despite the limitations of VF testing, OCT could best guide treatment decisions when imaging was considered in the context of perimetric findings. True progression could be reasonably inferred in a patient whose VF parameters were within normal limits but for whom a change was occurring in the VF guided progression analysis (GPA), statistically significant or not, so long as the VF GPA change was occurring in the same area as a statistically significant change in the OCT (Figure 4). Similarly, if manifestations of glaucoma were developing on OCT that were not yet statistically significant but that were consistent in shape and location with typical glaucomatous abnormalities, the physician could reasonably consider this to be representative of real progression.

Advanced Imaging Techniques and the Pathogenesis of Glaucoma

OCT angiography (OCTA) has provided insights into the relationship between neuronal and vascular changes in glaucomatous eyes. OCTA work by Huang and colleagues showed

significant differences in vessel density between glaucomatous and healthy eyes (Figure 5). (53) Glaucomatous eyes were found to have a significantly lower superficial vascular complex (SVC) vessel density at the macula than healthy eyes. In contrast, no significant difference was found in vessel density of the intermediate and deep capillary plexuses at the macula. In this study, a macular area with low perfusion in the SVC corresponded in shape, size, and location to areas of detectable GCC thinness and VF defects. (53) The SVC has been found to supply blood to the nerve fiber layer and ganglion cell layer. Thus, these studies suggested that vascular changes associated with glaucoma occurred preferentially among the vessels that feed the superficial layers of the retina. (52) A limitation of this work was the possibility that the measured vascular change was representative of a reduction in vessel perfusion rather than loss of vessel density, as OCTA would have been unable to differentiate the two phenomena.

It is important to distinguish whether the vascular findings were a cause or consequence of glaucoma progression, not only because of the implications for the broader understanding of glaucoma pathogenesis, but also because this distinction will guide the future clinical use of OCTA; vascular changes may prove to be a very early indicator of glaucomatous progression or a biomarker of advanced disease. The fact that the macular vascular abnormalities assume the shape and location of the GCC abnormalities suggests that the vascular density is reduced due to the loss of neural tissue, and not the other way around. The shape of the GCC abnormality is thought to be based on an insult at the lamina cribrosa, creating an expanding arcuate RNFL defect. Vascular supply would have no reason to take this shape, except as it is not required for nourishment or waste product removal in the RNFL or RGC layers. The fact that it is specifically the superficial vascular complex that is affected again indicated the relevance to neural loss. While macular superficial vascular plexus density clearly responds to inner retinal burden, as opposed to being the cause of neural loss, longitudinal studies of lamina cribrosa and papillary vasculature may yield further insights as to the role of blood flow in glaucoma pathogenesis, as this is the actual initial proposed site of glaucoma injury.

New Directions

Through use of both OCT and multi-modal magnetic resonance imaging (MRI), a recent study demonstrated that structural changes in glaucoma were not limited to the eye but also occurred in the brain (Figure 6). Further, there was a strong relationship between clinical ophthalmic assessments of glaucoma progression and MRI-based measurements. These eye and brain changes, which included inner retinal layer thinning, optic disc cupping, and visual cortex activity reduction, were present prior to detectable VF loss. In this study, the previously-described tipping points were recapitulated for RNFL, GCIPL, and ONH cup-to-disc ratio – the points at which VF abnormalities (i.e., mean deviation) became detectable in addition to structural defects. Interestingly, a similar segmented model of progression emerged in the relationship between VF threshold and MRI blood-oxygenation-level-dependent (BOLD) brain activity in the primary visual cortex; that is, there was a tipping point after which lower primary visual cortex BOLD signal corresponded with a reduced VFI, and before this point, VFI remained normal regardless of BOLD signal. Within the visual cortex, metabolic MR spectroscopy revealed that choline metabolism was increasingly abnormal with more advanced disease, suggesting that dysfunction of the

cholinergic nervous system in the visual pathway may be associated with the pathophysiology of glaucoma. (54)

Through a modification to adaptive optics scanning light ophthalmoscopy (AOSLO) – off-axis detection in two-photon excitation fluorescence – Rossi and colleagues were recently able to capture images of individual RGC somas. This feat had previously eluded the capabilities of AOSLO, owing to the near-transparency of the inner retinal cells. A limitation of this approach admittedly resulted in images with lower quality in humans than in monkeys. (55) Work by Miller and colleagues visualized of GC somas and axons with singly scattered light. Key strategies for accomplishing this included linking adaptive optics to OCT to create AOCT, overcoming motion blur with 3D subcellular image registration, and leveraging each cell's individual, mobile organelles as a natural “contrast agent”. (56) Advances such as these may enable tracking of RGC loss on a cellular rather than composite level in the near future, providing a more sensitive approach to detection of progression.

Conclusion

In contrast to the subjective assessments of the past, ophthalmic imaging provides objective, accurate, reproducible, quantitative data that can be tracked with rigorous statistics. As innovation in imaging techniques allows more precise visualization and objective quantification of ocular tissues and structures, glaucoma and its progression will be detectable earlier than ever before. Given the understanding that, once damaged, an optic nerve is increasingly susceptible to further damage (57–59) early detection of progression and subsequent escalation of treatment is paramount to preservation of vision and reduction of the risk of blindness for glaucoma patients. Advances in methods of image interpretation will also improve glaucoma care worldwide, as novel segmentation algorithms will standardize interpretation of structural eye abnormalities and changes in objective and quantitative terms. As such, as ophthalmic imaging technology becomes progressively more portable and affordable, it could enable any ophthalmologist in the global community to evaluate the ocular structure in glaucoma at the level of an expert observer. This standardization will foster excellence in the level of care for patients globally.

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Figure 1.
An early iteration of the Helmholtz ophthalmoscope, 1852. Courtesy of the “Joint Library of Ophthalmology Moorfields Eye Hospital & UCL Institute of Ophthalmology”. (Used with permission.)

Figure 2.

An 1854 illustration of a glaucomatous optic disc by Eduard Jaeger, drawn to depict protrusion and swelling, Jaeger's interpretation of glaucomatous disc change. The image was originally published in his text, *Ueber Staar und Staaroperationen* (Wien) (Used with permission.)

Figure 3.

AUROC for the best parameters obtained using three objective, quantitative methods of structural assessment demonstrate the superiority of OCT (inferior average thickness, AUROC = 0.91) over scanning laser polarimetry with enhanced (TSNIT, AUROC = 0.87) or variable (TSNIT, AUROC = 0.81) corneal compensation. Originally published in Sehi M, Ume S, Greenfield DS. Scanning laser polarimetry with enhanced corneal compensation and optical coherence tomography in normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci.* 2007;48:2099-2014. (Used with permission.)

Figure 4. Visual field results (a) and OCT RNFL GPA reports (b) for a representative patient. These studies illustrate that, even when early abnormalities on VF or OCT are not statistically significant, one can be reasonably certain that real progression is occurring when changes are occurring in corresponding areas for both tests.

Figure 5.

Data from a representative eye with glaucoma detectable on perimetric testing. The first and second columns display 6×6 mm en face angiograms from nonprojection-resolved OCTA and projection-resolved OCTA, respectively. The white arrows highlight the focal decrease in vessel density in a superior arcuate pattern in the superficial vascular complex (SVC) and all-plexus PR-OCTA images. The ganglion cell complex map (second image in third column) and visual field pattern deviation (third image in third column) demonstrate defects in corresponding locations. Of note, as might be expected, a corresponding decrease in

vessel density was not found in the PR-OCTA for the intermediate capillary plexus (ICP) or deep capillary plexus (DCP). Originally published in Takusagawa HL, Liu L, Ma KN, et al. Projection-resolved optical coherence tomography angiography of macular retinal circulation in glaucoma. *Ophthalmology*. 2017;124:1589–1599. (Used with permission.)

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Eye structures and brain activity are impaired prior to visual field loss in glaucoma

Figure 6.

Assessment of the relationships between perimetric visual function and (a) structural measures of the of retina and ONH (b) visual cortex activity as measured by MRI blood-oxygenation-level-dependent (BOLD) signal revealed that each of these relationships can be described by broken-stick (segmented) models. That is, this study demonstrated that functional impairment in terms of visual field progression occurs only after a “tipping point” in term of other measurements of glaucoma damage, and this finding holds true not only for measures of ocular structure (tipping points were 76.9 μm for RNFL [95% confidence interval (C.I.) = 67.9 to 86.0 μm], 59.6 μm for GCIPL (95% C.I. = 54.5 to 64.7 μm) and 0.81

for cup-to-disc ratio (95% C.I. = 0.79 to 0.83)), but also for measures of brain function (topping point was BOLD = 0.58% for upper visual field stimulation (95% C.I. = 0.34 to 0.82%) and BOLD = 0.61% for lower visual field stimulation (95% C.I. = 0.30 to 0.92%)). Red line represents the spline fit, and the black line represents the broken stick fit model. (*p < 0.05, **p < 0.01, ***p < 0.001: Davies' test for statistically significant difference in slope between segments). Originally published in Murphy MC, Conner IP, Teng CY et al. Retinal Structures and Visual Cortex Activity are Impaired Prior to Clinical Vision Loss in Glaucoma. Sci Rep. 2016;6:31464. (Used with permission.)

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Table 1

Early historical events in the evolution of glaucoma diagnosis.

Date	Event
400s BC	Hippocrates' <i>Aphorisms</i> includes the first written record of glaucoma
300s BC	Aristotle proposes that the color of an eye is dependent the amount of water within it
100s AD	Galen defines glaucoma as a discoloration of the pupils due to fluid shifts in the eye; he draws the optic nerve as a hollow structure
500s	Aetius describes two categories of glaucoma: a defect of the lens and a defect of the pupil
1510s	da Vinci notes the cornea and aqueous bend light and the temporal VF extends 90° from fixation
1626	Banister suggests the relevance of eye pressure to glaucoma
1668	Mariotte describes the blind spot
1673	van Leeuwenhoek draws first illustration of a peripheral nerve
1752	Daviel presents results of more than 200 cataract extractions
1755	Zinn contests the notion that the optic nerve is a hollow structure
1807	Young specifies the dimensions of the visual field
1826	St Yves describes clinical features of advanced glaucoma in <i>Nouveau traité des maladies des yeux</i>
1830	Mackenzie delineates six stages of glaucoma in <i>Practical treatise on the Diseases of the Eye</i>
1851	von Helmholtz invents the ophthalmoscope
1851	Mueller describes depression of the optic disc in glaucoma
1854	Jaeger illustrates swelling of the optic disc in glaucoma
1855	Weber describes the glaucomatous optic disc as "cupped"
1856	von Graefe proposes incorporation of visual field assessment into clinical practice
1860	Schwalbe discovers anatomical connection between anterior chamber and ciliary veins
1867	Weber invents the first applanation tonometer
1870	Leber describes the aqueous pathway
1879-1890	Priestley Smith suggests that glaucoma damage is due to vascular and metabolic changes in addition to mechanical forces; he later proposes that narrowing of the angle predisposes to glaucoma
1907	Trantas promotes gonioscopy as routine diagnostic technique
1920	Seidel refines Leber's filtration theory to account for colloid osmotic pressure of plasma proteins
1945	Hans Goldmann invents the hemispheric bowl perimeter

Date	Event
1950	Hans Goldmann introduces the Goldmann tonometer

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