Chapter No. 11

Future Glaucoma Instrumentation: Diagnostic and Therapeutic

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Core Messages

- Technological devices for the diagnosis and treatment of glaucoma are being developed and improved upon continuously.
- Intraocular pressure measurement techniques are needed that are less invasive, more accurate, less dependent on corneal thickness and ocular biomechanical properties, and available to the patient for home monitoring. Ideally, IOP measurement devices would provide measurements over 24 hours, like a Holter monitor for the eye.
- The future of ocular imaging is to provide accurate and precise objective quantitative measurements of the structure and function of both the anterior and posterior segments of the eye..
- Objective methods for accurately testing a patient's visual field more accurately would be extremely beneficial for assessing ocular function and for tracking a patient's progression.
- Telemedicine and automated diagnosis techniques are two computerized systems that may improve physicians' diagnostic capabilities in the future.
- Development of implants for improving anterior chamber fluid flow and drug delivery may improve glaucoma surgical techniques.
- New surgical instruments are enabling surgical techniques that were previously difficult or impossible.

1) Why are improvements in glaucoma technology necessary?

Glaucoma is a complex disease, with a variety of factors playing into its diagnosis and treatment. Because of the wide array of data that can be obtained about this disease, medical technology and instrumentation continues to play an important role in the assessment of the glaucomatous disease state and its treatment. The current state of ocular imaging, functional assessment, and surgical treatment has been discussed in previous chapters. This chapter aims to go beyond that, to assess what needs still should be met, and how glaucoma instrumentation could meet them.

Much of the future of glaucoma diagnostics focuses on obtaining objective measurements of glaucoma severity and progression, because current assessment is mainly subjective. Diagnostic instruments will probably never replace a trained glaucoma specialist, but may be able to provide such consistent, clear objective information that ophthalmologists will be able to identify and treat the disease at the very earliest stagesfirst indication of glaucoma, and prevent the disease from progressing to the point of affecting the patient's vision.

As device development technology is able to produce smaller, more complex devices, the possibility for surgical treatment for glaucoma using micron-scale devices is expanding. Stent and shunt technology is developing rapidly far beyond its initial uses in areas such as cardiology to uses in ophthalmology to improve aqueous outflow. Moreover, the development of development of surgical tools is enabling the incorporation of novel procedures. The pharmacokinetics of drug delivery is becoming better understood, leading to the possibility of extended, well-controlled release delivery systems for the eye. It may be possible that future devices are able to safely and reproducibly lower intraocular pressure, without the side effects and compliance problems inherent in medicalmedication treatments today.

The managementfuture of glaucoma will change as instrumentation designed to diagnose and treat it changes. In the ideal future, we would be able to detect and cure the disease before it causes any effects whatsoever, perhaps through genetic testing or other methods of diagnosis and gene therapy to repair or replace aberrant genetic code.. It is understood that earlier treatments are more effective, and pose less risk of progression, with less intense treatments necessary. This is becoming increasingly possible with new instruments and techniques, which can detect changes in the structure of the eye before functional loss occurs, such as imaging devices. As implants for treatment become available, and are smaller and easier to implement in patients, these techniques may help glaucoma patients move away from frequent tedious eye drops which effect that might be affected by adherence. The future of instruments for glaucoma treatment and diagnosis will depend greatly on future research discovering the root causes of the complex disease of glaucoma.

2) How can current techniques of intraocular pressure measurement be improved, and what is available that shows promise for the future?

Measurement of intraocular pressure (IOP) is a valuable component of a standard ophthalmic examination, because IOP has been shown to be the major causal risk factor for glaucoma. Unfortunately, However, the types of tonometry instruments most commonly used currently all have some inherent limitations that leave room for improvement in the future. Applanation tonometry requires corneal anesthesia, and is not suitable for uncooperative children or patients with corneal irregularities,damage due to the corneal contact necessary for this cornea contacting nature of the method. Pneumatonometry, which is essentially applanation tonometry as well can be used in children, where it may provide a more accurate measurement than Goldmann tonometry, and in patients with irregular corneas. Applanation tonometry is significantly affected by the corneal biomechanical properties of the patient including thinning or thickening of the cornea.It is also significantly affected by the corneal properties of the patient such as thinning or thickening of the cornea. Air-puff tonometry is non-contact but its accuracy is more questionable than the contact methods, and is also affected by corneal properties. Transpalpebral tonometry through the eyelid does notdoesn't require corneal contact but it can be difficult to obtain a consistent, accurate result with this technique. Schiotz tonometry, though rarely performed, is extremely portable, lightweight and simple, but is highly affected by scleral rigidity and intraocular gas.

Electronic indentation tonometry, rebound tonometry, dynamic contour tonometry, and the Ocular Response Analyzer are newer techniques that are currently available, and they attempt to address some of the problems with other methods. Electronic indentation tonometry (Tono-Pen; Reichert, Inc., Depew, NY) is a form of applanation tonometry, using a strain gauge to electrically acquire IOP measurements, and is actually not new at all. The McKay-Marg tonometer of over fifty years ago was such a device, but is no longer available, and has been shrunken down to a small, portable handheld device in the form of the Tono-Pen.. The advantage of the electronic indentation tonometry Tono-Pen device is that it can be used in a variety of positions on the subject because it is compact and lightweight. However, it is still subject to the same corneal property effects as other types of applanation tonometry, and accuracy is less than optimal.. Rebound tonometry (iCare Tonometer; Tiolat Oy, Helsinki, Finland) also involves contact with the cornea, but rather than several seconds of applanation, an ultra-light probe touches the cornea gently for just a fraction of a second, so a more comfortable measurement can be taken, without need for topical anesthetic. Also, the device is portable, like the Tono-Pen and the tips are disposable, providing a sterile measurement easily in each patient. The small size of the contact area (this technique was originally designed for use on rats and mice) is another advantage, allowing for pressure measurement on a localized unaffected area of the cornea in the case of patients with corneal damage. The portability and ability to use it without anesthesia makes it more feasible for out-of-clinic monitoring of IOP. However, it is also believed to be affected by corneal properties, though possibly to a lesser degree than applanation tonometers.

Dynamic contour tonometry (DCT, PascalPASCAL; Ziemer Ophthalmic Systems AG, Port, Switzerland) attempts to minimize the effects of the corneal properties of the patient. Dynamic contour tonometry appears similar to Goldmann applanation tonometry, but rather than applying variable force, it applies a constant force to match the contour of the device tip, which is concave with radius 10.5mm, approximating the shape of the cornea. As the pressure changes on the sensor inside the tip, this is calculated as a change in the electrical resistance, which corresponds to the IOP. Once the tip is matched with the surface of the cornea, the device takes 800 measurements over 8 seconds to find an averaged IOP. By matching the tip to the cornea, this technique can reduceneutralize the effects of the individual's corneal properties. This is reflected by the fact that the "LASIK effect", where individuals' IOP is measured to be significantly lower post-refractive surgery due to the change in corneal structure, is not present when DCT dynamic contour tonometry is used to measure IOP in contrast to the findings with Goldmann applanation tonometry;. [1] however, other confounders do still exist that affect the accuracy of DCT's IOP measurements.

The Ocular Response Analyzer (Reichert, Inc., Depew, NY) calculates variables that describe the corneal properties in addition to calculating a cornea-compensated IOP. It uses a pulse of air to depress the cornea inward to a slight concave shape, and monitors the changing shape as it depresses, then bounces back. The 2 pressures at which the cornea is applanated (flat) – as it moves inward, then back outward – are calculated, and the difference is used to define the corneal hysteresis. Figure 1 contains a graphical representation for this. The corneal hysteresis is defined by the viscous-elastic properties of the cornea, which are believed to be the major factor affecting IOP measurement.[2] Using this information, the Ocular Response Analyzer provides a cornea-compensated IOP. This device also has the advantage of being non-contact with the cornea, since the corneal deformationdepression is done by air.

One of the main problems of IOP monitoring clinically is that it consists of just a single measurement, often taken only once every three to six months. Because IOP can vary substantially throughout the day, these single measurements might not truly gauge how effectively the glaucoma is managed. The ultimate IOP measuring device would be one that is not affected by the corneal properties, does not require corneal contact and allows for continuous measurements.

Summary for the Clinician

- There are a wide variety of methods for measuring IOP, but many have the problem of being affected by corneal properties, and most rely on several seconds of corneal contact, which can be uncomfortable or difficult to perform..
- Some newer methods (electronic indentation tonometry and rebound tonometry) are portable devices, unlike standard Goldmann applanation tonometry, which improves their flexibility.
- Dynamic contour tonometry and the Ocular Response Analyzer both attempt to adjust for certain corneal biomechanical properties, aimingattempting to calculate IOP that is not confounded by dependent on the cornea.

- Rebound tonometry and the Ocular Response Analyzer minimize corneal contact, resulting in no need for anesthetic, while providing a more accurate measurement than traditional air-puff tonometry.

3) Is continuous management of IOP possible through telemedicine?

The future of glaucoma IOP management would be an accurate, portable, easy-to-use device that could be purchased by glaucoma patients, or loaned to them by their eye care professionalglaucoma clinics, so that patients could self-monitor their IOP, similar to people with high blood pressure. By recording frequent IOP measurements, they could provide much more detailed information to their doctor through telemedicine than the current single measurements taken in the office.

At this point, one such device has been developed and is clinically available, the Proview tonometer (Bausch and Lomb; Rochester, NY). It uses a unique approach of having a device that the person presses on their eyelid until they see a phosphene (a dark spot with a ring around it) caused by the pressure of the device transpalpebrally and transsclerally mechanically stimulating the retina, and then the patient can they read the pressure of the device and record the pressure from the device. Its accuracy has been found to be substantially poorer than typical clinical measurement methods, but is an important first step toward developing an accurate self-monitor for IOP. [3] It is not the first or only home tonometer, but is one that is generally commercially available.

A unique approach to this problem of frequent IOP monitoring would be the use of a an implantable device or device incorporated into a contact lens or some other implantable device that could transmit IOP data electronically to a detector, which could then can record the information for the ophthalmologist. This would require less action by the patient and minimize the amount of human error in the measurements. One potential problem with patient self-monitoring is failure to comply fully with their treatment protocol if they are finding their IOP to be "normal". If measurements are recorded electronically for submission to the physician directly, patients mightwill be less likely to haveknow their IOP and let it affect their treatment compliance affected by their continuously monitored IOP.. Also, tonometers can be difficult for many patients to use on their own correctly, so a method with minimal input needed from the patient would be of benefit.

The approach of incorporating IOP measurement into a contact lens has been tested to measure changes in corneal curvature with an imbedded micro strain gauge. A contact lens would be less invasive than an implant, which could be integrated into an intraocular lens placed during cataract surgery. However, the internally placed device would be less subject to corneal property changes, and could be more accurate because of measuring pressure directly, rather than the indirect method of measuring corneal curvature change. Initial development has been done with both techniques but much more research is needed to make this technology safe, affordable, and comfortable so it would be clinically feasible. [4]

These constant IOP monitoring devices will be very relevant for the future of glaucoma and of telemedicine in this field.. Developing systems to get continuous IOP data cleanlyclearly and efficiently to physicians will be as difficult and important as developing the tonometer itself. With the large amounts of data that would be generated

by a system like a continuous IOP monitor, it is vital for the informationit to be able to be summarized clearly, whether graphically or otherwise, so physicians aren't overwhelmed by lists of numbers of noisy data.

Summary for the Clinician

- IOP varies substantially over time so that a single measurement once every six months is not sufficient.
- The future will require patients to measure their own IOP periodically and record it for their physician so a more accurate assessment can be made.
- Telemedicine will provide a better way to provide this information clearly and concisely to the clinician once an easy to use, reliable method is developed for continuoushome measurement of IOP.
- Contact lens or more likely implant based methods for monitoring and recording IOP information electronically will provide continuous IOP measures without the need forcould aid in reducing patient compliance. This continuous monitoring information will allow physicians to assess diurnal IOP variation and better manage risk factors associated with glaucoma progression. involvement in the measurement.

4) How will new photographic techniques improve glaucoma diagnosis?

The most recent substantial changes in glaucoma instrumentation have come in the form of ocular imaging, and this continues to be a major area of research focus in the glaucoma field. This includes technologies ranging from stereoscopic discdisc photography, to scanning systems such as optical coherence tomography in its various forms. Improvements are still being made in both the way these devices acquire images, and the way the data can be processed to gain more information.

Disc photographs were the earliest method available for objectively capturing an image of the optic nerve head as , similar to that seen during clinical examination. While systems for capturing these images have become fairly standardized, there continues to be a need for a standardstandard method of analyzing and quantifying the structures seen in these images. At this point assessment is subjective and variable, even when the disc photographs are read by expert observers.

The two main types of parameters that would be useful to quantify for glaucoma are retinal nerve fiber layer (RNFL) defect measurements and optic discdisc parameter measurements. Semi-quantitative scales have been developed to assess the amount of retinal nerve fiber defect in a disc photograph, but this is done manually by a trained physician examining the photograph, and is prone to inter-observer variability. [5-7] A method of quantitatively analyzing the amount of RNFL defect automatically has been proposed by Lee and associates using image processing techniques to locate the optic disc and plot the intensity of pixels around the disc.. [8] The area of defect is then determined by comparing the intensity plot of the RNFL and the first derivative of the intensity plot. For clinical use, this and other methods of locating and quantifying the extent of RNFL defects must be established as reliable and reproducible.

Stereo disc photographs also hold substantial information about the optic nerve head, though automatic quantification is scarce due to the complexity of disc margin detection. Moreover, the variety of cameras used clinically, with a variety of displacements between the two images and changes in magnification further complicate disc parameter calculations. Much initial research has been done by Xu and Abramoff, among others, into modeling of the three-dimensional discdisc structure, as well as peripapillary disc features such as blood vessels. [9, 10] A demonstration of this process can be seen in Figure 2. However, these methods still need improvement and stabilization, especially in the case of poorer quality images and subtle abnormalitiescases, where current quantitative methods may not be sensitive enough to detect glaucomatous damage.

An importantThe primary reason for developing a quantitative method for evaluating looking at stereo disc photos the large amount of legacy data available. Photography is photography is the oldest and the most common technology for imaging the eye, so there is the potential of developing the most extensive longitudinal data with this modality. This gives researchers the largest data set to look at glaucomatous progression, and gives clinicians the most history for many of their patients. If a consistent, accurate method of

quantifying this data can be applied, significant knowledge about the progression of the disease can be obtained.

Summary for the Clinician

- Optic disc photographs are the oldest objective method of recording the optic disc appearanceimaging for glaucoma, but current clinical interpretationuse of them is primarily subjective.
- Quantification of nerve fiber layer defects objectively through image processing techniques holds potential for clinical use.
- Three dimensional digital representation of the optic disc based on stereo-photographs could provide objective quantitative optic disc information.
- The use of photography with objective methods of analysis could provide the most extensive longitudinal information, due to photography'sits clinical use for a longer period of time than any other imaging technique.

5) How is optical coherence tomography going to provide new anterior segment information?

Optical coherence tomography (OCT) is the ocular imaging technique that has shown the most new promise for a variety of important uses in glaucoma and other eye diseases.. In addition to the now common clinical use of time-domain OCT, spectral-domain OCT (SD-OCT) is quickly gaining clinical popularity. OCT is being applied to the anterior eye, in addition to the more common retinal imaging use.

OCT has been used in the anterior eye since 1994, [11] but only recently has it been gaining common use clinically for evaluation of the cornea and anterior chamber, and for angle assessment in glaucoma cases. It has the advantage of being much more comfortable than ultrasound biomicroscopy (UBM) because it is non-contact, uses near infrared light (which is invisible to the patient), and able to acquire scans with the patient in a sitting position, and is able to provide a much highergreater resolution scan, though with lower penetration beyond the iris. This prevents imaging of the ciliarycilliary body, an important target tissue in many cases of glaucoma evaluation. However, the non-contact aspect of the OCT makes it more appropriate for imaging of filtering blebs or angle imaging just after surgery than UBM. It could also be of great benefit for use in children or other patients who might not be willing to have a UBM. [12]

The primary clinical anterior segment specific OCT device currently available is the Visante OCT (Carl Zeiss Meditec, , Dublin, CA), a time domain system specifically for anterior eye imaging, with a longer wavelength light allowing for more penetration into the sclera and iris than would be available at the wavelengths typically used to image the retina. The future of anterior segment OCT is to move towards spectral domain devices for scanning, which would allow for faster scans with higher resolution. This would allow a near cellular level view of the cornea and detailed information on angle structures such as the Schlemm's canal. Currently, anterior segment spectral domain OCT is only possible clinically with add-on systems to retinal-based devices.

Summary for the Clinician

- Anterior segment OCT is non-contact, and is therefore more comfortable and more suitable for patients just after surgery or for children.
- Anterior segment OCT also provides higherbetter resolution than UBM.
- Anterior segment OCT However, it lacks the depth of penetration of UBM, making visualization of structures behindstructure beneath the iris impossible.
- Current clinical anterior segment OCT systems are time domain OCT, but the future is will be anterior segment spectral domain OCT, with improved speed and resolution.

6) How does SDOCT improve our ability to visualize ocular disease?

The primary advantage of using SDOCT in either the anterior or posterior segment of the eye is the ability to acquire images with higher resolution (up to 3μm in the eye) and faster scanning speed (up to 5550,000 A-scans per second) than the time domain OCT (resolution; 8-10μm, scanning speed: 400 A-scan/sec) . This enables the development of new scanning modes such as three-dimensional scans that can be used to visualize eye structures. However, because this iteration of the the technology isis new, software to fully utilize the data acquired by the machine, such as three-dimensional visualization and segmentation, is still in its infancy. Inspecting individual B-scans is a sufficient method to look at the horizontal structure of the eye tissue, but visualization of specific vertical layers across the scanning region is difficult due to motion artifacts. Methods for vertical. Methods for vertical alignment of the scans may prove helpful in being able to sample the scanned area in any desirable direction and to view en-face or C-scan image.. Visualization of the various forms of three-dimensional OCT data can be seen in Figure 33.

While producing images from the three-dimensional data is valuable, OCT holds the unique potential to provide quantifiable data from the three-dimensional data set. For example, in the anterior segment, if a three-dimensional scan across the whole anterior chamber is gathered, the size of the angle 360 degrees around the eye could be measured, along with other angle quantities. This information could be displayed graphically, providing glaucoma specialists with quantifiable angle measurements that can be easily interpreted and used to identify optimal surgical sites. Three-dimensional data sets of the retina provide a multitude of possibilities for segmentation leading to automated quantifiable information regarding the thickness of retinal layers, or other retinal landmarks, such as quantifying drusen in macular degeneration, or determining the geometry of the optic nerve head as it relates to glaucoma. Currently the segmentation and analysis of three-dimensional SDOCT data sets is a very important area of research in optical coherence tomography. As segmentation algorithms improve, SDOCT will provide clear thickness maps for the layers corresponding to glaucoma damage. Another potential advantage of the three dimensional dataset is the possibility to align one set of scans to another. This would enable a physician to obtain measurements at the same location between visits with higher precision, thus improving the ability to detect even minute structural changes over time.

Summary for the Clinician

- SDOCT is able to create entire three-dimensional data sets, rather than just the simple multi-line patterns of time-domain OCT.
- Software for visualization and interpretation of these three-dimensional data sets is still in the beginning stages.
- Segmentation and quantification methods will provide more accurate information from the scanned area.

7.

7) What other OCT techniques have been developed for research use that may become clinically relevant?

In addition to processing OCT data in new ways, there are several methods of acquiring OCT data in new ways that may have potential for future use in glaucoma. New optical techniques have been applied to SDOCT, including swept-source imaging, adaptive optics, and the calculation of functional data such as blood flow and changes in reflectance of retinal layers due to light exposure. All of these may have future implications for glaucoma imaging. SweptSwept-source OCT (SSOCT), is a frequency-domain OCT method with some similarities to SDOCT. [13] SDOCT uses a broadbeam light source to acquire reflections across a variety of frequencies, where SSOCT uses a single tunable light source that emits a single frequency at a time, which can be rapidly swept across a wide range of frequencies. This method provides a much faster acquisition rate, more than 200,000 A-scans/second, as opposed to SDOCT's rate of 16,000 A-scans/second. This allows for a much faster scan time and reduced reduced motion artifacts. DDue to the highhigh sampling raterate of SSOCT, multiple rapid scans can be averaged to reduce the noise level and improve the signal. Currently these systems are expensive and limited to axial resolution of around 10μm because of technological limitationslimitations of the tunable laser. . However, as tunable laser technology improves, the price and resolution will improve, and these devices may be clinically relevant.

SDOCT is valuable clinically because of the large improvement in axial resolution it provides compared to time-domain OCT. However, transverse resolution in traditional SDOCT systems is still limited, due to the natural aberrations in the cornea and lens affecting the reflection from the retina. However, the addition of adaptive optics to SDOCT systems will help improve this in the future. Adaptive optics is the use of a wavefront sensor to identify these aberrations and then correct for them using deformable mirrors. Adaptive optics has been used with OCT [14] as well as confocal scanning laser ophthalmoscopy [15] and fundus imaging, [16] and can provide sufficient transverse resolution to image photoreceptors in vivo. [17] There is hope that adaptive optics can provide sufficient resolution to visualize ganglion cell bodies, which are typically too transparent to see without adaptive optics. This could provide a method for more accurately assessing retinal neuron death due to glaucoma, by assessing actual cell body loss rather than interpolating the amount of damage based on the thinning of the axons of the retinal nerve fiber layer.

OCT and perhaps other imaging techniques will also provide the opportunity for monitoring functional aspects of the eye with glaucoma, including blood and aqueous flow and functional activation. As discussed in previous chapters, retinal blood flow is believed to be relevant to many eye diseases including glaucoma. Doppler OCT is in the beginning stages of being established for measuring the ocular blood flow in real time and in-vivo.. As a better understanding of the velocities measured by Doppler OCT can be developed, it may become a valuable tool for measuring the rate and volume of blood flow in the eye in baseline and following interventions that affect blood flow. Fluid flow measurement is also relevant for glaucoma in the case of the angle, though Doppler

measurement in the aqueous outflow system would be much more complicated than measuring contained, primarily laminar flow in blood vessels. With much progression in the technology, Doppler OCT assessment of flow may become as clinically useful for glaucoma as Doppler ultrasound is for measuring vascular flow elsewhere in the body, such as the carotid artery.

Initial research has been begun using the spectroscopic information gained by SDOCT to examine the oxygenation of the retinal blood supply.. [18] The red to infrared broadband wavelength allows the determination of the ratio of oxygenated blood in the vessels, comparing reflectance at different wavelengths, using techniques somewhat similar to a pulse oximeter. The oxygenation of the blood in the retina may also be related to glaucoma and other retinal diseases..

Another area of interest in OCT is functional OCT - gaining information about the function of the retinal tissue beyond the blood vessels. [19] There is evidence that the reflectance of certain layers of the retina (particularly, the outer segments of the photoreceptors) increases when exposed to white light after being dark-adapted. This technology is in the very early stages, with tested areas of stimulation no smaller than a hemisphere, but it may be able to be used to map function across the retina in patients affected by glaucoma. This would provide an objective method of examining function if the resolution of tested areas can be mapped small enough. It should be noted that thethe change in signal is very small (10-15% of baseline amplitude) and it will need to be amplified into a more robust signal if this is to be clinically relevant, but the advantages of an objective, repeatable functional test would be significant.

Summary for the Clinician

- Swept source OCT is a technique that is similar to SDOCT, but is able to acquire data substantially faster, though its axial resolution is limited by tunable laser technology to 10μm.
- The incorporation of adaptive optics into SDOCT systems can greatly improve transverse resolution by removing the effect of optical aberration in the lens and cornea.
- Doppler OCT can allow for retinal blood flow measurements.
- Spectroscopic information from various wavelengths within the broad spectrum of SDOCT can provide retinal oxygenation data.
- Changes in reflectance of the photoreceptors when exposed to light after being dark adapted may be valuable in the development of functional OCT.

8) Will objective measurements of visual field be possible?

Currently, the most common techniques for visual field assessment are not objective, but rather, utilize patient responses to map out their visual field. Perimetry suffers from substantial inter-visit variability for each patient, resulting in significant difficulty in tracking or defining progression in a slowly developing disease like glaucoma. Changes to visual field protocols, such as decreasing the time of test taking, can decrease some of the variability, but the future calls for a more objective method.

The primary initial attempts to measure the electrical signals of the functioning retina are multifocal electroretinography (ERG) and multifocal visual evoked potential (VEP). These tests provide an indication ofof the functional properties of the eye without the need of subjective input. ERG is gathered with electrodes on the cornea and around the eye, and the signal is processed to determine the responses corresponding to certain areas of the visual field. VEP maps the visual field based on the visually related cortical signals from electrodes placed on the scalp. Electrical noise due to poor electrode contacts, poor grounding or ambient electrical sources can often affect the ERG output. The technician can minimize the first two during the examination, but the third issue means the ERG must be acquired in a room shielded from sources of 50/60 Hz electrical interference. Eye movement can also cause substantial errors, with inconsistent fixation causing smearing of the response between loci. VEP suffers from similar effects, with other complications inherent in the electroencephalogram process.

Smaller test targets and improvement in the recoding threshold level would allowallow the detection of localized damage and thus further improveimprove the utility of these devices for glaucoma assessment. Using eye-tracking methods may alleviate some of the artifacts appearing due to the eye movement and allow for changing fixation, so the electrical signals can be processed with their dependence on the location of the subjects' fixation.

Imaging techniques may also provide potential for objective functional assessment of the eye. Besides the functional OCT optophysiology measurements discussed previously, a Retina Function Imager has been developed based on traditional fundus imaging technology which uses the changes in the optical properties caused by the metabolic state of each specific area of the retina. Other optical methods have also been proposed for monitoring retinal changes, such as reflectance changes of photoreceptors during adaptive optics scanning laser ophthalmology. [20] Imaging methods may be more comfortable for the patient than the electrodes of ERG and VEP, and may provide better resolution, so this remains an important area of research for clinical glaucoma.

Summary for the Clinician

- Current visual field techniques are subjective and have substantial patient inter-visit variability.
- ERG and VEP provide an an assessment of visual function.
- However, these methods are subject to several artifacts, such as electrical interference, movement, or poor electrode placement.

- Functional imaging techniques may also someday be valuable for determining localized retinal function.9) How can all the diagnostic data be combined into an automated diagnosis?A primary purpose for recent advances in glaucoma diagnostic instrumentation is to provide a variety of valuable information to ophthalmologists who incorporate these results into a diagnosis. In order to differentiate between apparently conflicting results from different devices, ophthalmologists require substantial training and experience. The amount of information now available helps ophthalmologists make more educated decisions about a patient's glaucoma without as much subjective judgment as it required in the past, but there is not yet a cohesive method of knowing how to combine all the data available. Working toward systems for automated diagnosis will help solve this. A risk calculator that predicts the risk of developing glaucoma was introduced recently using demographic as well as clinical examination information. However, this method does not take into consideration the important information obtained by imaging devices that might substantially improve the performance of these calculators.Automated diagnosis information based on comparison to a prior normative data set is already available individually for many glaucoma instruments. For example, Heidelberg Retina Tomography III (Heidelberg Engineering; Heidelberg, Germany) provides a Glaucoma Probability Score ranging from 0 to 1 based on a machine classifier algorithm implemented on the data set, as well as Moorfields Regression Analysis and several Linear Discriminant Analysis parameters that are used to classify subjects as healthy or glaucomatous using multiple parameters. An example of the clinical representation of each these parameters can be seen in Figure 4. OCT and visual field devices provide comparison to an age-matched normative database that can classify the subject as inside or outside normal limits. However, the automated diagnoses of each individual machine may provide results that appear to contradict one another, and currently the physician must rely on his or her experience to assess what the true situation is for their patient. It would be beneficial if a system were developed that could take the information from various devices (clinical and demographic information, visual fields and imaging results) and process it to yield the risk of glaucoma disease or glaucoma progression, taking all data into account simultaneously. However, there is much more that must be learned about how different devices interpret and output data from the same person to know how the risk calculator should use and weigh information gained by each device. This system would have the advantage of bringing all ophthalmologists up to the level of glaucoma specialists.

9) How can all the diagnostic data be combined into an automated diagnosis?

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However, the automated diagnoses of each individual machine may provide results that appear to contradict one another, and currently the physician must rely on his or her experience to assess what the true situation is for their patient. It would be beneficial if a system were developed that could take the information from various devices (clinical and demographic information, visual fields and imaging results) and process it to yield the risk of glaucoma disease or glaucoma progression, taking all data into account simultaneously. However, there is much more that must be learned about how different devices interpret and output data from the same person to know how the risk calculator should use and weigh information gained by each device. This system would have the advantage of bringing all ophthalmologists up to the level of glaucoma specialists.

Summary for the Clinician

- Automated diagnosis is already possible for individual machines, through comparison to normative databases or discriminatory models based on experimental testing.
- However, it can be difficult for clinicians to distinguish important information from each of the diagnostic devices if their results appear contradictory, without significant experience with each one.
- Future development of systems to integrate information from different devices into aa glaucoma risk profile would be very beneficial.

10) How can visualization be improved during surgery?

Ocular surgery is an extremely delicate process, with challenges far beyond many other surgical fields, due to the small, sensitive nature of the structure of the eye. It can be difficult for the surgeon to clearly view the surgical site, and imaging techniques may aid in this.

Canaloplasty (iScience Interventional; Menlo Park, CA) is a new surgical technique that has been greatly aided by the development of an ultrasound probe that can be used during surgery to image the angle as an illuminated microcatheter is fed through it. The combination of the visualization using the ultrasound and the illuminated tip of the microcatheter enables more complete visualization of catheterization of Schlemm's canal. This device utilizes ultrasound for use during surgery by eliminating the need for a continuous water bath, which is obviously not feasible during surgery, through a unique probe design. The probe features a disposable sterile tip with an acoustic window in it covered by a thin film. Water is inside this tip behind the film, with acoustic coupling occurring when the film contacts the eye. [FIGURE] The ultrasound, with center frequency of 80 MHz, is able to image to an imaging depth of 2-4 mm at 25-μm axial resolution. Like with an optical device, there is a tradeoff between imaging depth of penetration and image resolution. The development of a handheld probe using other imaging technology, such as endoscopic imaging or OCT, would be beneficial for higher resolution imaging, either intra-ocularly though a small endoscope, or externally.. Some progress has been made in the use of endoscope technology for imaging during goniotomy, where it can be used to visualize structures despite cloudiness in the cornea. However, the procedure is not as frequently performed as a trabeculectomy, and the invasive nature of an endoscope may interfere more during surgery than it is able to aid during the procedure. An external imaging source could provide more information about the entire anterior segment during surgery if it can be developed into a smaller, handheld type of device, similar to the ultrasound biomicroscopy probe.

In addition to imaging of the structure of the aqueous outflow system, the ability to image the aqueous flow and quantify it during surgery would be of benefit. This could give the surgeon immediate feedback which can lead to surgical modification while the procedure is conducted. Doppler ultrasound and OCT may hold potential for feedback to surgeons with visualization of changes in flow. Currently, Doppler ultrasound and OCT has only been used on ocular blood vessels, [21] because their larger size and velocity makes it easy to measure flow in them, but it may be possible to measure flow along Schlemm's canal as resolution increases. Even if this technology cannot be presented in a compact handheld unit for during surgery, it could be useful post-surgery to assess how the surgery has affected the aqueous outflow system.

Summary for the Clinician

- An ocular ultrasound system has been developed for use during surgery, without use of a water bath for acoustic coupling as in traditional UBM.
- Endoscopic imaging or development of a handheld OCT probe could also aid visualization during surgery in the future.

- Imaging of the aqueous outflow system during or just post-surgery could help in assessing the surgical outcome.

11) How can shunt and stent technology be applied to the eye??

In recent years, a variety of stent or shunt devices have been proposed for aqueous drainage procedures These devices aim to decrease ocular pressure by allowing easier fluid flow from the anterior chamber most often to the suprachoroidal space where it can be filtered away, though some devices are testing other filtering routes such as increasing flow directly to the eye's own aqueous outflow system.. These devices take different approaches to allowing greater aqueous outflow, and have displayed varying degrees of effectiveness.

Most shunt/stent devices for glaucoma operate under the same principle as a trabeculectomy, diverting fluid into the sub-conjunctival space to form a filtration bleb. For example, the Ex-PRESS Miniature Glaucoma Device (Optonol Ltd., Neve Ilan, Israel) is a stainless steel, less than 3-mm-long, 400-micron-diameter (27 gauge) tube, which acts as a shunt. The implant is placed under a scleral flap, with the tip penetrating into the anterior chamber. The structure of the device and its ocular placement can be seen in Figure 5. It has been found to have similar IOP-lowering effects to trabeculectomy, with fewer incidences of hypotony complications. [22] However, there is potential that the outer end of the tube can cause erosion and become exposed, resulting in the need for device removal, and complications are more common in advanced, complicated glaucoma cases. Other frequently used clinical devices with similar benefits and complications such as the Ahmed Glaucoma Valve (New World Medical, Inc., Rancho Cucamonga, CA) , which attempts to use a valve system to control the suprachoroidal outflow, and the Molteno Implant (Molteno Ophthalmic Ltd, Dunedin, New Zealand) are also continually undergoing improvement to provide sufficient lowering with minimal hypotony and other complications.

The SOLX Gold Shunt (SOLX, Inc., Waltham, MA) uses a similar approach but rather than bringing the aqueous outflow out of the eye through the sclera, the fluid is brought suprachoroidally, underneath the sclera. It is a flat plate shaped device made of gold, with multiple micro-tubular channels that connect the anterior chamber and suprachoroidal space. The device and its placement can be seen in Figure 5. The natural pressure differential between these two areas maintains the flow across the device. As one of the newest glaucoma devices, its efficacy isn't yet established in published literature.

The iStent (Glaukos Corp, Laguna Hills, CA) trabecular bypass stent uses a different approach to reducereduce resistance to aqueous outflow by providing a direct conduit between the anterior chamber and Schlemm's canal, avoiding the resistance of the trabecular meshwork. The device and its placement can be seen in Figure 5. This method seeks to avoid creating an unnatural method of filtration by using the natural outflow from Schlemm's Canal. This device must be placed carefully to avoid dislocation, and minimal results have been published about the utility of the device, but initial results seem promising. [23]

All of these devices have the approach of structurally altering the aqueous outflow pathway in order to reduce the ocular pressure. One of the aims of using one of these

devices is to provide a more consistent surgical technique with less variability in outcome between surgeon and patients and with fewer complications and side effects. However, because glaucoma is a diverse disease, one specific stent or shunt may not work as effectively in all patients. The future of these surgical implants may be that they will be adjustable allowing for tailoring the device for each patient's needs, such as changing the diameter of the channels or tube. Adjustable stents and shunts are becoming more common in cardiology.

Drug eluding stents are another example of technology in another field of medicine that might be relevant to glaucoma instrumentation development. Many of the drug-eluding stents designed for use in coronary arteries are treated with a drug that prevents cell growth over it which can re-occlude the vessel. Similar complications can occur in the eye, so this technology could be relevant for glaucoma.

An ultimate drainage device will be a small and simple device that would require minimal surgical skills to insert it into the eye with the minimal resistant level to prevent hypotony. The device should be tunable so it can be adjusted to the needs of each patient and various levels of intraocular pressure.

Summary for the Clinician

- A variety of stent and shunt devices are becoming available for clinical trials to help improve glaucoma surgical outcomes by allowing more controlled aqueous outflow.
- Adjustable and drug eluding stent technology that is currently available in cardiac and vascular surgery medicine may someday be applicable to ocular shunt or stent devices.

12) How can drug delivery and treatment compliance be improved?

Pharmaceutically, there are adjustments that can be made to improve compliance, such as fixed combinations of drops and single daily dosage, rather than multiple different drops a day. Also, drops with fewer side effects will tend to have better adherence to the treatment. Education about the need to take the medication correctly can help increase adherence. However, improvements in delivery systems may help improve adherence as well. Many patients may have trouble getting the drops into the eye, or putting the correct number of drops in their eye. A more accurate method of dispensing eye drops, such as a spray or change in the shape of the dispenser, may aid in this. Electronic monitoring devices attached to the bottle may also help increase the adherence to treatment with timely reminder of the patient.

DrugDrug-eluding implants may serve as a method for getting glaucoma medications directly into the eye with improved treatment adherence and efficiencyefficiency as compared to daily self-medication with drops.. . Intra-vitreal controlled release devices have been developed and FDA approved for cytomegalovirus retinitis and uveitis (Vitrasert and Retisert; Bausch and Lomb, Rochester, NY), and other devices are being developed for intravitreal placement, including a biodegradable dexamethasone implant for persistent macular edema (Allergan; Irvine, CA) and a helical coil containing triamcinolone for diabetic macular edema (SurModics: Eden Prarie, MN). Figure 6 contains images of the Retisert device as well as the approximate scale of it. Similar devices for the dispensing of medications such as prostaglandin analogs, beta-adrenergic receptor antagonists, or Alpha2-adrenergic agonists could be beneficial in glaucoma. Ocular stents could also act as a platform for controlled release drug delivery that would improve patient adherence.

The two FDA approved implants are reservoir style implants, which are possible due to the extremely small daily drug doses needed to be effective when provided intravitreally, allowing for use for up to 1000 days. The dexamethasone implant is made up entirely of a biodegradable polymer mixed with drug. The helical coil implant is made of a non-reactive metal alloy that can be coated with drug for released delivery, with the helical coil providing the greatest surface area for drug coating. These implants are all for retinal diseases, not glaucoma, but they raise the possibility that direct drug delivery could be possible as a long treatment module for glaucoma. Implants for glaucoma treatment could either take the similar form to these previous ones, being implanted intravitreally, or in anterior segment implants similar to current glaucoma shunts and stents. Some of these devices can be inserted into the eye fairly simply through a paracentesis. This could lead to simpler treatments compared to complex eye drop routines, with fewer complications compared to more invasive surgeries.. Sub-conjunctival injections would be another method of improving compliance somewhat invasively, but this compliance would be variable, depending on how often these injections were required because of the dependence of a physician's visit for the injection, and this would not be an optimal treatment method for children. Further study would be required to make this clinically viable.

Patients with chronic, slowly progressing diseases like glaucoma often have the poorest adherence to medical treatment, because they do not immediately feel the effects of not using their medication. Patients tend to underestimate the severity of their disease, until it has substantially progressed, and in a disease such as glaucoma where the damage is irreversible, this is currently posing a significant treatment challenge.

Summary for the Clinician

- There are several devices that could help improve adherence with eye drop medication treatment, including devices to improve drop dispensation and electronic monitors to track compliance.
- Ocular drug delivery implants have been developed and are being tested for retinal disease, but this technology may be helpful for glaucoma drug delivery asas well.
- These slow release devices could improve patient adherence by replacing or decreasing the need for eye drops.

13) How are new surgical tools enabling new surgical techniques?

Recently new surgical tools have been developed that allow for surgical procedures previously unavailable with standard ophthalmic surgical tools. These new tools allow for site-specific interventions in the anterior chamber of the eye to provide greater aqueous outflow, by using micro-scale operating instruments.

The iTrack Microcatheter (iScience Interventional, Menlo Park, CA) combines an optical fiber with a polymer tube, strengthened by a support wire, to create a catheter whose tip can be illuminated for visualization, and can be used to provide various ophthalmic solutions through the lumen. The tip and shaft are designed specifically to prevent tissue damage or trauma in the eye, and its flexibility allows the catheter to be fed 360 degrees around Schlemm's canal during the canaloplasty. In addition to accessing Schlemm's canal, the catheter is valuable for accessing the angle during cataract surgery, or to aid in performing viscocanalostomy or deep sclerectomy. Initial clinical study of this new technique has so far been promising as a safe and effective procedure. [24]

The Trabectome (NeoMedix Inc.; Tustin, CA) is another device that has enabled a new type of surgery for open-angle glaucoma. It is used to remove a section of the trabecular meshwork through electrocauterization, to allow more fluid flow through this section. Through its microtip, which incorporates the cauterization electrodes, irrigation, and aspiration systems together, it is able to cauterize and clear tissue minimally invasively. The device and its positioning during use can be seen in Figure 7. A curved protective footplate that prevents damage to surrounding tissues, as well as guiding the tip along Schlemm's canal, protects the tip. Use of this technique has been shown to produce a cleaner severance of the trabecular meshwork, with less reclosure as compared to goniotomy. [25] This has translated clinically into subjects with lower IOP and less need for medication post-surgery as time progressed. Many of the complications seen with trabeculectomy have not been seen with this technique, and the use of this technique does not preclude trabeculectomy if the initial Trabectome procedure is not successful in lowering the IOP sufficiently. [26]

Both these new surgical instruments demonstrate the potential for newly developed devices to provide completely new surgical techniques. The primary progression towards the future of glaucoma surgical devices will probably not be devices to aid in current common surgical techniques such as trabeculectomy, but rather to develop new devices that can provide new surgical options. Developing new, safer, effective ways of decreasing ocular pressure is an important role for the future, and as micro-manufacturing processes improve, we can expect a trend towards even less invasive surgical procedures.

Summary for the Clinician

- Standard surgical procedures typically have standard tools that are not being actively modified for the future.
- The future of the development of new surgical tools is to allowallow new surgical procedures not possible without these new devices.

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Figure Legends:

Figure 1: Three Dimensional Rendering from Stereo Disc Photographs.
Using camera type, magnification, and distance between images as input information, the stereo photographs can be mathematically rendered to provide a three-dimensional model of the optic nerve head, which can then be measured objectively.

Figure 2: Three Dimensional Optical Coherence Tomography Data.
Upper left corner represents 5 selected B-scans from a raster set consisting of 200 B-scans. These can be represented in a 3D reconstruction that can be sliced along any plane (upper right shows entire 3D reconstruction and reconstruction sliced through optic nerve head). Summing the intensities along each A-scan creates the en face image in the lower left. The 3D data set can also be used to show just a certain thickness along a chosen contour to isolate specific layers like the retinal nerve fiber layer (lower right). C-scan includes only data taken within the light blue region of the B-scan above it. The location of the B-scan within the 3D data set is the red line. The light blue line is currently identifying the right side of the disc margin at that B-scan.

Figure 3: Corneal Hysteresis for the Ocular Response Analyzer.
These graphs demonstrate how corneal hysteresis, a measurement of corneal visco-elastic properties, is calculated. Pressure is increased on the cornea smoothly by a pulse of air that indents the central cornea from convex to concave, followed by the cornea rebounding to convex. The two points where the cornea is applanated (flat) are found optically, and the pressure difference between them defines corneal hysteresis. Figure 3a presents a typical healthy cornea. Figure 3b presents a cornea post-LASIK surgery, where corneal hysteresis is reduced due to weakening of the cornea from flap creation during surgery, making it less capable of absorbing the energy of the air pulse. This weakening affects tonometry results. P1=Pressure on cornea during applanation from convex to concave, P2=Pressure on cornea during applanation from concave to convex, CH=corneal hysteresis.

Figure 4: Single Device Automated Diagnosis Based On Comparison to Normative Database.
Heidelberg Retinal Tomography III software provides two primary methods for providing a diagnosis of inside normal limits, outside normal limits, or borderline. A glaucomatous patient's results are presented. Glaucoma Probability Score (GPS; left) is based on an automatically fit disc shape model independent of disc margin tracing. This patient is classified as outside normal limits overall and in all sectors, with a GPS value of 0.86 overall, indicating a 86% chance of this patient having glaucoma. (GPS value not shown). The Moorfields Classification (right) is based on the operator-traced disc margin, and this patient shows a mixture of all three classifications overall and sectorally, with the final classification of outside normal limits.

Figure 5: Glaucoma Stents and Shunts

Figure 5a is the Ex-PRESS Miniature Glaucoma Implant, which allows flow from the anterior chamber to the suprachoroidal space. Three slightly different versions are available, depending on the surgical needs. (Optonol Ltd, Neve Ilan, Israel)
Figure 5b is the iStent which allows flow to bypass the resistance of the trabecular meshwork by creating a direct connection between the anterior chamber and Schlemm's Canal. (Glaukos Corporation, Laguna Hills, CA)
Figure 5c is the SOLX Gold Shunt, which bridges the anterior chamber and suprachoroidal space with microchannels. (SOLX, Inc., Waltham, MA)

Figure 6: Bausch and Lomb Retisert
This drug-delivery implant is used to treat chronic non-infectious uveitis affecting the posterior segment of the eye. A scale is provided to identify the size of the device. (Bausch and Lomb, Rochester, NY)

Figure 7: Trabectome
This glaucoma surgical device uses electrocauterization of the trabecular meshwork to allow freer aqueous flow into Schlemm's canal. The structure of the tip (right) also incorporates irrigation and aspirations ports to clear away the cauterized area. The protective footplate is fed along Schlemm's canal to prevent damage to the canal itself while the current between the electrodes ablates trabecular tissue (left) (NeoMedix Inc. Tustin, CA).