

# EGRET(+)

**an extended European Glaucoma  
Research and Training Network**



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From the start of 2016 – mid 2020, the **E**uropean **G**laucoma **R**esearch **T**raining program and the European Glaucoma Research Training program-plus together funded a total 25 Early Stage Researchers (ESRs) across Europe to work on important questions related to glaucoma. The ESRs have acquired new, quantitative knowledge on glaucoma and the aging visual system, and have applied this to boost innovation in glaucoma care in both public and private sectors. This has been accomplished by extensive research in different disciplines: basic vision science, epidemiology, genetics, neuroimaging, eye-tracking and psychophysics.

- **“Improving functional tests for glaucoma”**
- **“Using genetic information to improve our understanding of glaucoma”**
- **“Improving the assessment of brain structure in glaucoma”**
- **“Improving intraocular and intracranial pressure assessment in glaucoma”**

This leaflet presents the situation by the end of the two programs. It provides a short summary of at least one major output from each ESR and describes its potential future relevance to healthcare, science, society and industry. If you would like to know more about our research and latest progress, please visit [www.egret-plus.eu](http://www.egret-plus.eu) or [www.egret-program.eu](http://www.egret-program.eu) for further details and links.







## Glaucoma

Glaucoma is the most common age-related neurodegenerative eye disease in western society and one of the four major blinding eye diseases. Glaucoma is an insidious disease that – when untreated or detected too late – leads inevitably to blindness, resulting in a profound loss of quality of life for the affected individual and in major costs to society.

In the European Union, approximately 6 million people have glaucoma. Current treatment – which aims at lowering eye pressure – can slow deterioration but does not halt the process. Approximately 15% of glaucoma patients still become blind.

The conventional view of glaucoma is that of an eye disease in which an elevated eye pressure damages cells of the retina, initially resulting in visual field loss and ultimately in blindness.

The studies in EGRET(+) were motivated by the notion that this classic view is far too simplistic. For example, in their experiments, the fellows tested whether glaucoma is a disease that is not restricted to the eye, but may also involve increased pressure inside the skull. Furthermore, they have examined which genes are implicated in glaucoma and studied the resemblance to Parkinson's disease. Moreover, the fellows in the extended EGRET network designed new and improved tools that can be used in the diagnosis of the complex disease that glaucoma is.



## *“Improving functional tests for glaucoma”*

Visual field testing, or perimetry, is crucial for the assessment and progress monitoring of glaucoma. Perimetry tests require patients to fixate their eye, keep their head still and to respond to a small flashing light in their field of view using a button press. Yet patients report the current techniques to be time consuming, tiring and difficult to complete. These issues may result in unreliable examinations, an impaired glaucoma detection or overestimation of the eye condition.

### Testing fitness to drive a car with Ocusweep

**Iris Tigchelaar**  
*Ocuspecto*

Glaucoma has a negative influence on driving performance, yet glaucoma patients can be safe drivers. Visual field tests are currently used to assess fitness to drive a car and differentiate between the driving capabilities of patients. **Tigchelaar** and colleagues argue that using visual fields is too simplistic as it does not consider the patient's compensation skills.

To overcome this lack, they tested whether the Ocusweep® can be used to measure the fitness to drive. They showed that this multifunctional device provides measures of both visual and cognitive functioning that re useful to predict fitness to drive.

**Iris Tigchelaar's** experimental set-up with the driving simulator (in the back) and the Ocusweep (in the front).

### Using eye-movements to screen for visual field defects

**Daniel Asfaw, Birte Gestefeld & Rijul Soans**

*CITY University London & University Medical Center Groningen*

Current visual field tests require patients to fixate their eyes, keep their head still and respond to a small flashing light in their field

of view by using a button press. This is often difficult for patients to perform especially for the very young, very old, and patients with cognitive impairment.

**Asfaw, Soans** and colleagues studied whether it is possible to use eye-movements and virtual reality to screen for various types of vision loss, including glaucoma. By analyzing the characteristics of eye-movements they were able to distinguish reliably between various types of vision loss.

**Gestefeld** and colleagues have been able to reconstruct simulated visual field defects based on eye-movements that were measured while a person watched short movie clips. Furthermore, in collaboration with Royal Dutch Vision, they showed a great potential for Virtual Reality for improving rehabilitation training of patients with large visual field defects. Lastly, in collaboration with the Donders Institute of Nijmegen, she helped to improve the software for a stereo eye-tracking system, thereby enhancing the applicability of the system in clinical practice.

Together, Asfaw, Soans, and Gestefeld developed visual field tests that are more entertaining, quicker, cheaper, more comfortable and more intuitive than the ones currently used in practice.

**Rijul Soans and Jacqueline van den Bosch** demonstrating Soans's experimental setup to a patient. With this set-up eye-movements can be measured whilst being in a Virtual Reality environment.

### Using big data from clinics to assess the care of glaucoma patients

**Stephen Kelly**

*CITY University London*

Electronic medical records are increasingly being used for patient management in eye clinics in the UK, replacing traditional paper records. **Kelly** and colleagues studied these digital records of routinely collected data to better understand patient management in glaucoma clinics.

For example, they examined thousands of visual field records collected over 15 years. Their work highlighted aspects in the records that seem to be informative and able to identify patients in the clinic that are at higher risk of going blind.



## Making perimetry better

**Catharina João**

*University Medical Center Groningen*

Self-reports indicate that glaucoma patients see well with good light, but have poor vision in the dark or in rapidly changing light conditions.

**João** and colleagues studied the effect of test conditions on the visual field measures. Perimetry was performed with normal and reduced lightning, normal and a rapidly changing background light, and black and white stimuli.

She showed that perimetry can be made better by adapting the test situation to those situations that are reported by the glaucoma patients to be difficult, such as under low lighting.

## Evaluation of current and new techniques to assess the visual field

**Giorgia Demaria**

*University Medical Center Groningen*

**Demaria** and colleagues questioned the feasibility and practicality of the current ways of visual field testing, in particular with older patients. They evaluated seven different visual field tests, including four newly developed/experimental ones, that examine the visual field in different ways.

The test battery included devices which used eye-tracking and thus required no motor response from the patient; which didn't require the patient to sit uncomfortably due to a chin and headrest, or which examination was shorter and thus less tiring for the patient.

Most tests showed to be well feasible and provided useful clinical information. Yet, the diagnosis process for glaucoma can be improved when using tests tailored to the condition of the patient.

## Motion detection in glaucoma

**Lorenzo Scanferla**

*University Medical Center Groningen*

Seeing moving objects might be hampered in glaucoma, especially in the dark, even in those with an apparently normal visual field.

**Scanferla** and colleagues explored this observation by examining the visual perception of moving lines and showed that patients require the line to move a much greater distance before the movement was detected than control subjects. This effect was even greater when testing was performed under low light levels.

Together with Joao, they also explored vision in glaucoma using dichoptic stimulation, i.e. different stimuli presented simultaneously to each eye. With this, they challenged the idea that glaucoma patients should have normal vision as long as their binocular visual field, i.e. the visual field based on the input of two eyes, is intact. They showed that two damaged eyes together do not provide normal vision, even when the binocular visual field is intact.

## Visual brain assessment without a need for visual stimulation

**Azzurra Invernizzi**

*University Medical Center Groningen*

In glaucoma patients, some visual brain areas are no longer fully stimulated due to a loss of visual function at the level of the eye.

**Invernizzi** and colleagues investigated whether the brain of a glaucoma patient adapts to these changes in visual input. They used functional MRI and developed optimized analysis techniques to map the brain's functional organization in people who are "at rest" and have their eyes closed.

Since this does not require visually evoked brain responses, it avoids many of the complications that occur when studying the visual brain of patients with limited vision. Therefore, it can be used to objectively assess the functional organization of the visual brain of glaucoma patients.



# "Translational genetics in glaucoma"

Glaucoma has a strong genetic factor, which means that if someone in your family has glaucoma, then there is a higher probability that you will also get it. This suggests that inherited genetic defects crucially contribute to the presence of the disease.

## Identification of glaucoma genes

**Valeria Lo Faro**

*University Medical Center Groningen*

To date, the number of genes and the genetic factors that are known to be involved in glaucoma are far from being definite.

**Lo Faro** and colleagues explored these genetic influences and showed a role for mitochondrial genes and genes named CDKN2B, FOXC4 and ATOH7, which all have been implicated in the degeneration of retinal cells.

Since such degeneration is considered a clear sign of glaucoma, the identification of these candidate disease genes contributes to our understanding of the genetic mechanisms underlying glaucoma.

## Glaucoma and organoids

**Philip Wagstaff**

*Amsterdam Medical Center*

**Wagstaff** and colleagues focused on translating the genetic information of disease genes into function and pathology, and ultimately towards developing retinal therapies. They constructed lab-grown 'miniature eyes', known as retinal organoids, that mimic aspects of real-life human eyes.

Using gene editing techniques, they simulated a genetic model of glaucoma in the organoids. The effects of the mutations and how they cause glaucoma are currently being studied. This study provided extraordinary insight in the regulation and interaction between glaucoma candidate disease genes.

This is highly relevant for understanding disease pathology, implementing improved genetic risk calculations and developing rational genomics driven glaucoma therapies.

**Philip Wagstaff** has grown retinal ganglion cells "in-a-dish" as an initial precursor to growing 'miniature eyes' and used these to examine the effects of genetic modification on cell development.

## A glaucoma risk score

**Anna Neustaeter**

*University Medical Center Groningen*

Genes are not the only decided factor when it comes to glaucoma, but we can use genetic knowledge to predict who may be at higher risk for getting glaucoma. **Neustaeter** and colleagues developed a genetic risk score for glaucoma. She is currently investigating the feasibility of using this risk score in early glaucoma screening by applying this to the population-based LifeLines cohort that screens participants for the presence of glaucoma.

They expect glaucoma to be five times more likely in those with a high risk compared to those with a low risk. If confirmed, this genetic risk score will make early detection of glaucoma more efficient, and thus saving sight and reducing the burden of glaucoma.

## Heritability of eye-diseases

**Nigus Asefa**

*University Medical Center Groningen*

Heritability is the proportion of individual differences in a trait or disease that can be attributed to genetic factors. In a large population-based study, **Asefa** and colleagues showed that the heritability of glaucoma is between 65-81% and that of traits closely related to glaucoma ranges from 43% (for eye pressure) to 81% (for thickness of the cornea).

These high heritability values confirm that people with a family history of the disease are at a much higher risk than the rest of the population. The study also showed that in addition to traditional risk factors, such as elevated eye-pressure, family history, age, and ethnicity, low heart-rate variability and high blood pressure may be important to consider while screening for glaucoma.



**Anna Neustaeter** has now started the first prospective glaucoma screening trial "EyeLife" where inclusion is driven by genetic risk.



# “Improving the assessment of brain structure in glaucoma”

It is well documented that glaucoma does not only affect the eye, but leaves its traces also in other parts of the visual system. This means that assessment of glaucoma should include the full visual pathway, from the eye to the brain.

## Long-term changes in the visual brain due to glaucoma

**Gokulraj Prabhakaran**

Otto-von-Guericke University Magdeburg

Several glaucoma patients continue advancing to further deficits despite receiving treatment.

This indicates involvement of part of or the entire visual system, including the brain, in glaucoma progression.

**Prabhakaran** and colleagues investigated the impact of long-term glaucoma on the organization of the visual brain. For this purpose, they used functional MRI to assess the fate of the brain that lost its retinal input.

The visual brain showed abnormal functional activity in the brain areas deprived of visual input, which might indicate reorganization of the visual brain.

## Progress in understanding glaucoma pathogenesis and its early detection

**Khaldoon Al-Nosairy**

Otto-von-Guericke University Magdeburg

A possible mechanism to assess damage induced by glaucoma is the electrical activity of the visual system in the presence of visual stimuli. **Al-Nosairy** and colleagues developed novel techniques which allow for the recording of electrical responses from the retina.

These recordings were obtained in combination with posture induced changes in eye-pressure. The new methods improved our understanding of glaucoma pathogenesis and have a potential for aiding early detection of glaucoma.

## What causes the brain of glaucoma patients to change?

**Shereif Haykal**

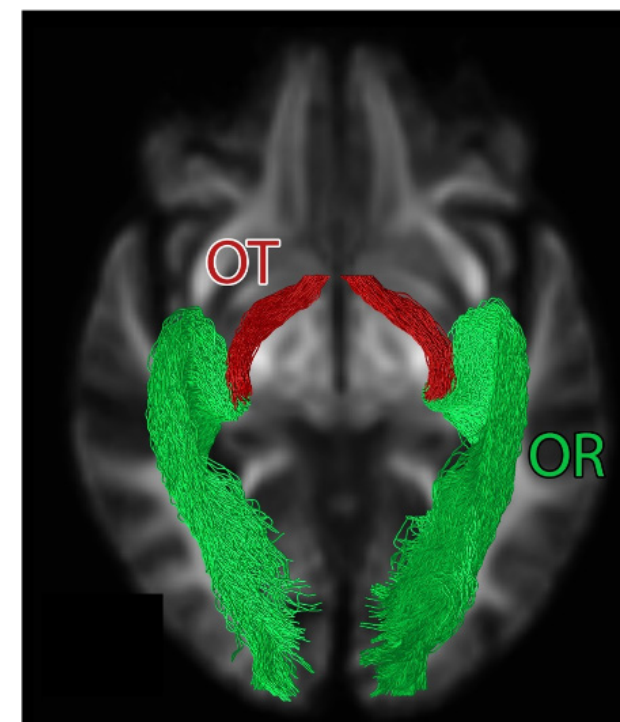
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The presence of brain degeneration in glaucoma patients, in addition to degeneration in the eye, is well documented. Yet, the source and nature of this degeneration has yet to be fully understood.

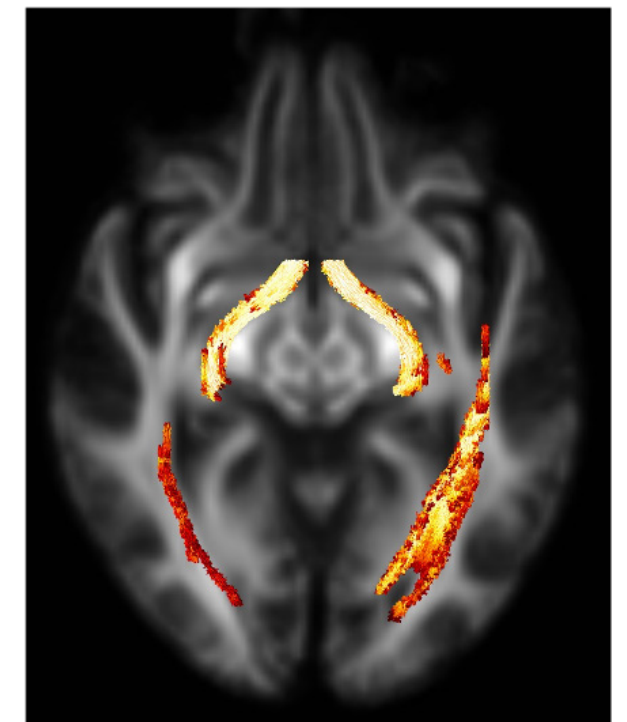
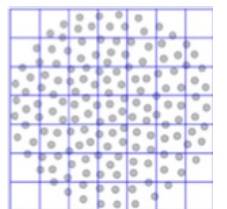
**Haykal** and colleagues applied MRI in combination with a new and very sensitive analysis technique and found that parts of the visual pathways closer to the eyes show signs of more advanced degeneration compared to parts that are farther away from the eyes and closer to the visual brain.

This shows that glaucomatous degeneration of the visual pathways most likely starts at the eyes and then spreads towards the brain. Future glaucoma therapies may therefore also consider limiting brain degeneration.

### Optic Tract (OT) Optic Radiation (OR)



### Fiber-bundle Density



**Shereif Haykal** delineated the two main visual pathway structures (left) and showed for both a lower number of axons (fibre density) in glaucoma patients (right).



## Imaging retinal layers needs standardised software

**Tuomas Heikka**

*University Medical Center Groningen*

Optical coherence tomography (OCT) is a non-invasive technique used to visualize the different layers of the retina. The thicknesses of these layers convey pivotal information for glaucoma diagnosis. However, measurements differ between different OCT brands and depend on the quality of the image. Heikka and colleagues compared OCT measures (of healthy, glaucoma, and eye-model) from different devices and with a range of image qualities. They showed that differences in layer thickness are mainly due to differences in software, not hardware.

This implies that interchangeability can be improved by using standardized software. Furthermore, current clinically used software can discriminate between glaucoma and healthy, but cannot stage glaucoma reliably making it unsuitable for the monitoring of disease progression. Therefore, Heikka developed a new bi-as-free software tool that segments the different layers of the retina and is currently investigating its usability in glaucoma progression detection.

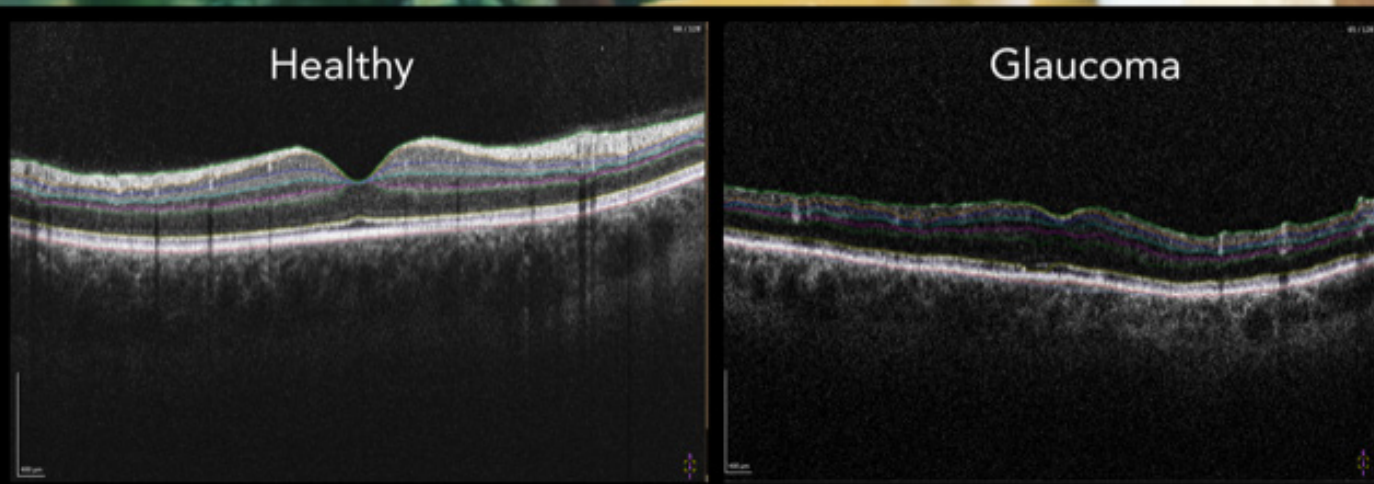
## The eye reflecting the brain in Parkinson's Disease

**Asterios Chrysou**

*University Medical Center Groningen*

Patients with Parkinson's disease (PD), a disease characterized by brain pathology, frequently complain about a variety of visual disturbances. **Chrysou** and colleagues investigated the visual properties of PD patients, thereby focusing on the retina. They showed that the retina of these patients (even at early stages) was thinner than those of healthy people.

Furthermore, this thinning showed resemblance to the thinning seen in glaucoma. Currently, Chrysou and colleagues are following PD patients over time to follow the progression of retinal damage, and how this is related to the development of brain pathology.



**Tuomas Heikka** compared the thicknesses of the retinal layers using different OCT machines. The images visualise the retina of a healthy person (left) and of a person with glaucoma (right) using the Canon OCT.





## *“Improving intraocular and intracranial pressure assessment in glaucoma”*

The classic concept of the primary cause of glaucoma is that of increased eye pressure. Not surprisingly, the only proven treatment option of glaucoma is the lowering of eye-pressure, or intraocular pressure (IOP). For that reason, monitoring IOP is an important aspect of glaucoma care. Yet, standard glaucoma care provides only a single IOP measurement approximately every three months.

Furthermore, the existence of glaucoma with normal eye-pressure suggests this concept of increased IOP is incomplete. One hypothesis is that the differences between eye-pressure (intraocular) and the pressure in the skull (intracranial) should be considered. Therefore, it is important to have reliable, non-invasive, and accurate tools that assess intracranial pressure (ICP). Currently, ICP is measured invasively using a lumbar puncture.

### **High blood pressure in glaucoma: the chicken or the egg?**

**Konstantinos Pappelis**

*University Medical Center Groningen*

In addition to high IOP, studies suggest that both high and very low blood pressure increase the risk of glaucoma. The presumed mechanism is a reduced blood flow in the optic nerve.

However, this relationship is difficult to study because a reduced blood flow could be both the cause or the consequence of glaucoma (chicken-egg paradox). **Pappelis** and colleagues have developed a new model to measure many blood-flow related features of the eyes of healthy subjects with different blood pressure profiles.

By combining these measurements, they are able to disentangle the chicken-egg paradox. Knowing the role of blood pressure is crucial for an effective management of patients with glaucoma that also have high or low blood pressure.



**Konstantinos Pappelis** and colleagues used Laser Speckle Flowgraphy to examine the changes in retinal blood flow.



## Influence of various physiological parameters and different time scales on intraocular pressure

**Vincenzo Pennisi and Jacqueline van den Bosch**

*Otto-von-Guericke University of Magdeburg and Implantsdata*

Continuous measures of IOP can be obtained through an implantable intraocular pressure sensor developed by Implantsdata®. **Van den Bosch** and colleagues investigated the utility of this novel pressure sensor in clinical settings. They showed that these sensors make it possible to assess IOP in detail, both by patients themselves when at home, but also by researchers in experimental settings. Such improved monitoring is of high value and can be used to assess the influence of various physiological and behavioral factors on IOP.

Using the same intraocular sensor, **Pennisi, van den Bosch** and colleagues studied the influence of such factors on the level and variability of IOP. Measures were obtained during simulated daily activities like light exercise, different breathing patterns, eye movements, and body positions. IOP was affected by eye movements and almost any physiological perturbation.

Understanding the relationships between physiological and behavioral factors and IOP will advance our knowledge of IOP physiology and pathophysiology.

**Jacqueline van den Bosch** examined the effect of gaze direction on eye pressure in glaucoma patients with an implanted eye pressure sensor. Gaze directions were guided using a laser pointer.



## Frequency selectivity of the inner ear

**Sina Engler**

*University Medical Center Groningen*

In order to improve the usability of emissions by the ear as a measure of ICP, it is important to have a better understanding of the functioning of the inner ear. One aspect of this is the frequency selectivity, the tonotopically encoding of acoustic sound frequencies, of the inner ear.

**Engler** and colleagues developed a new method to study the ear's production of tones (spontaneous otoacoustic emissions) that were recorded from the ear canal. So far, this measurement is the only automatic, objective and non-invasive way to assess frequency selectivity at the cochlear level in humans.

## No need for routine assessment of intracranial pressure

**Allison Loiselle**

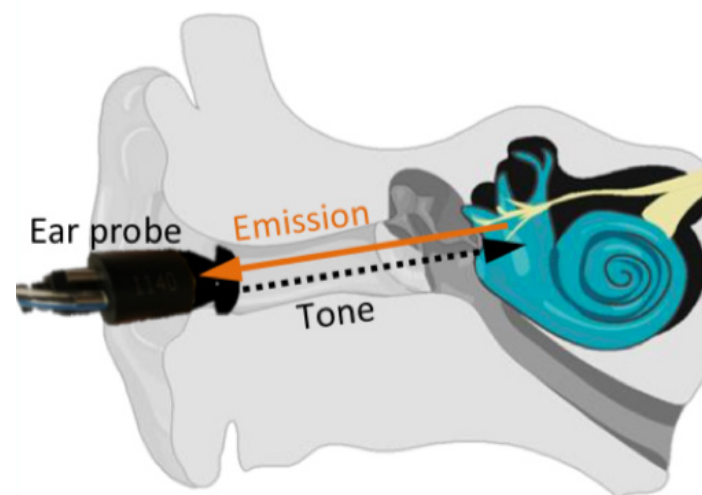
*University Medical Center Groningen*

Using changes in otoacoustic emissions as a proxy, **Loiselle** and colleagues examined differences in ICP between glaucoma patients and healthy controls. They showed that ICP does not differ grossly between the two groups. Interestingly, Loiselle found a lowering effect of diamox, a drug commonly used in glaucoma treatment, not only for intraocular pressure (IOP) but also for ICP. This suggests that diamox may not be a good treatment for glaucoma.

Lastly, Loiselle found a relation between glaucoma and tinnitus (ringing in the ears) and a role for a specific blood regulating molecule were uncovered.

With this current knowledge, routine assessment of ICP seems not needed in glaucoma patients. The role of the special molecule may open new diagnostic and therapeutic directions.

### Selectivity measurement



**Sina Engler** recorded spontaneous otoacoustic emissions by placing a probe in the ear canal.

**Allison Loiselle** used the Humphrey FDT to quickly screen study participants for glaucoma.





## Partners of EGRET(+)



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