Continuous IOP Monitoring: The Advance that will Enable all Others

Recent advances in glaucoma therapy are extending the runway between failed drugs and risky, morbid surgery, but they're only the beginning in a field that still has some significant unknowns. Perhaps the most disruptive innovation will come from monitoring technologies, since today, the inability to assess the most important parameter in glaucoma, IOP, beyond periodic visits to the physician's office, is a limitation that hampers decision-making and the efficacy of existing therapies.

Like patients with diabetes, glaucoma patients are asked to manage their own disease on a daily basis. They're required to be compliant with therapies prescribed on the basis of a single, isolated parameter—blood glucose levels, in the case of diabetes, and intraocular pressure in the case of glaucoma. But in the case of glaucoma, no self-monitoring paradigm exists, and that's another reason—beyond the unpleasantness and difficulty of administering eye drops—why glaucoma patients fail to comply with therapy. In the absence of noticeable symptoms and self-testing tools, patients don't get any feedback about how their medicine is helping, and many don't fundamentally understand that if they don't take their medications as directed, they are almost certain to progressively lose their eyesight.

Today, IOP is generally only measured quarterly (or so) when a glaucoma patient goes to the physician's office for a check-up. The standard method is Goldmann Applanation Tonometry, which, to describe it simplistically, infers IOP by measuring the force required to flatten the cornea. Therapy decisions are based on that in-office measurement of IOP, the patient's visual acuity, and the progression of visual field loss.

However, a single IOP measurement isn't necessarily informative. IOP levels fluctuate on a daily basis according to posture changes and circadian rhythms; studies have found that IOP rises during sleep and during the early morning hours, for example. IOP patterns also differ from patient to patient; studies have found that in some patients with only moderately high average IOP measurements, large daily fluctuations seemed to contribute to visual field loss. These variables, taken together with the inability to know whether a patient has complied rigorously with the prescribed therapy, make clinical decision-making hardly better than a guesstimate.

The Holy Grail in the field of glaucoma has long been a continuous IOP monitor that could reveal individual patient patterns of IOP, and numerous academic groups and a small number of companies have taken on the challenge. **Sensimed AG**, which was spun-out of the Swiss Federal Institute of Technology is selling *Triggerfish*, a contact lens containing a circular strain gauge that captures spontaneous circumferential changes at the corneoscleral area. *Triggerfish* claims to measure the 24-hour profile of ocular dimensional changes, a parameter that is supposed to correlate with the relative change of IOP. The soft contact lens also contains a microprocessor that communicates with a self-adhesive, disposable external antenna placed around the eye, from which data is transferred to a handheld recorder. *Triggerfish* is able to capture more than 86,000 data points over a 24-hour period, yielding an individualized profile of a patient's ocular volume change expressed in arbitrary units over that time period. The device, available in several countries (but not yet in the US), is approved for use during a single 24-hour recording session for the diagnosis and treatment planning of people with or at risk of developing glaucoma, and not for long-term continuous monitoring, at least not for the time being.

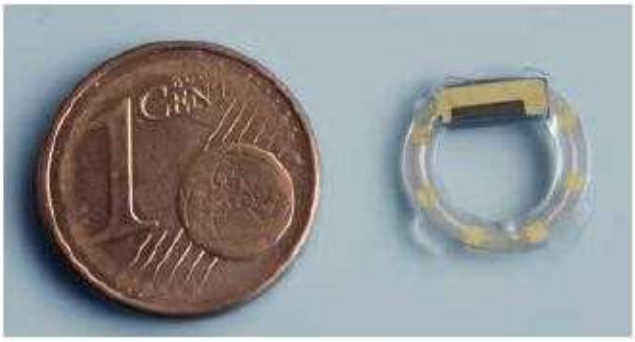
Other companies, for example **Solx Inc.**, **AcuMEMS Inc.**, and **Implandata Ophthalmic Products GmbH**, have undertaken the long journey to a long-term continuous IOP monitor. Of these, Implandata is the most advanced, as the only company with substantial clinical data in hand.

Implandata was founded in 2010 and has raised €6.2 million to date through the completion of its Series B round in September 2014, with a group of investors that includes Hannover Beteiligungsfonds, High-Tech Gruenderfonds, Peppermint Venture Partners, Enjoy Venture, ERP Startfonds of the KfW, and Born2Grow Venture Partners. It is

Figure 4

Implandata's EyeMate Implant

For Continuous IOP Monitoring



Source: Implandata Ophthalmic Products GmbH

well on its way to receiving a CE mark, which, the company hopes, will be granted soon after three month follow-up of its multicenter ARGOS-02 study, to be completed in the first quarter of 2016.

Implandata's *EyeMate* is a permanent implant that directly measures IOP (rather than inferring it through surrogate measures) with an array of capacitive pressure sensors. There is a thin, flexible membrane (a polyimide-based thin-film substrate) that is indented by pressure in the eye and a thicker, rigid base. When the cell membrane is mechanically deflected by pressure changes, the capacity of the cell changes according to the change in distance between the membrane and the base. "Our device actually measures pressure, and it quite nicely correlates to Goldmann Applanation Tonometry," says Max Ostermeier, a cofounder and General Manager of Implandata.

The implant is a flexible ring-shaped disc that is powered by an external reader using RFID-technology. The reader also receives data transmitted from the implant, and in the current product configuration, allows up to 3,000 measurements, which equates to about one month of measurements with a 15 minute interval between each measurement (*see Figure 4*).

The implant is encapsulated in a silicone rubber material to enhance its biocompatibility and durability inside the eye, with the goal of permanently providing accurate measurements. Ostermeier notes that the company has done accelerated bench testing and has demonstrated a life expectancy for the device of at least 30 years. "Unlike devices that have to be placed in blood or stressful areas, the eye is a nice environment for an implant like ours." Implandata has data out to five years in some patients, "And the sensors are still working nicely and precisely," says Ostermeier. In the first 20 patients implanted, he notes, "there was no single device malfunction, no need for explantation, and the technology is robust and safe."

Piggybacking on Cataract Surgery

For its first market, Implandata, like Glaukos, is targeting patients with glaucoma who are candidates for cataract surgery, so the surgical implantation of the monitor can piggyback onto an existing surgery. That makes its device eligible for 20% of cataract patients, or approximately 740,000 patients in the US, which is the number of patients undergoing cataract surgery who also have glaucoma, according to estimates from Glaukos.

Ostermeier explains the implantation procedure for *EyeMate*. "You do standard cataract surgery. You extract the lens, insert the IOL into the capsular bag, then through the same incision, you use our injector to insert the *EyeMate* implant, which is foldable, into the ciliary sulcus—not into the capsular bag, but right behind the iris and in front of the IOL."

That's the company's initial market, but it has plans to study other indications for future markets, including the secondary treatment of pseudophakic patients (those who have already had IOLs implanted during cataract surgery) and keratoplasty (or corneal transplant) patients, who frequently develop glaucoma secondary to the surgery. Ostermeier notes that high IOP is a frequent cause of transplant rejection. Also in the pipeline is a second product, an extraocular sensor to be placed in the scleral pocket or suprachoroidal space, which will be targeted to patients in earlier stages of glaucoma, in situations where intraocular implant placement is not advisable, or patients who haven't developed cataracts yet.

In the US, the company is now preparing an IDE study to test *EyeMate* in keratoprosthesis patients, which is somewhat of an "orphan" indication, Ostermeier notes, since there are only approximately 1,200 such surgeries in the US and 2,300 worldwide. But in these patients, the need for frequent IOP monitoring is crucial for the prevention of blindness from glaucoma, or from the hypotony and retinal detachment that can result from overmedication.

As noted, many academic and commercial efforts are putting their minds to the problem of continuous IOP monitoring, but Ostermeier believes it will be difficult for others

to catch up with Implandata. "The problem of a long-term implanted sensor is a tough one," he says, noting that he started working on this project in 2001, when it was under the aegis of the applied research institution Fraunhofer-Gesellschaft. "You have to make sure it is going to work over time—accurately and precisely in five and ten years. It won't work to implant something that loses accuracy or that needs to be recalibrated every few days." Ostermeier adds that the sensor needs to be robust enough to remain stable during temperature changes and under mechanical stress. "And you can't afford to have a bulky device inside the eye. It has to be accurate, stable, and as small as possible."

The Value of Data

The *EyeMate* system displays IOP data on the handheld reader, and that data can also be communicated to caregivers or the patient's physician via a separate GSM (Global System for Mobile Communication) module. The company has also developed a smartphone app so patients can look at their own pressure histories. "A patient can see that two days ago his IOP was 15 [mmHg] and 12, two weeks before that. " The app will also serve as a support system between the patient and doctor; patient-specific medication reminders can be set to direct the patient to take medications at certain times of the day when IOP tends to be higher. "It is not just an implant, but a whole digital system for remote patient management and supporting the care of patients," says Ostermeier.

Peppermint Venture Partners (PVP) invested in Implandata's Series A round in 2012. At the time, says Klaus Stoeckemann, PhD, managing partner and co-founder of PVP, the burgeoning area of mhealth began to highlight the data portion of the equation and the importance of "getting data out to a handheld device and sharing it among all the stakeholders. We saw that if Implandata could get the implant small and safe enough, the next piece would be getting the data uploaded to a portal, which is a very important part of the whole business model and for the utility of the device. That's why we felt it was the right company to invest in."

Stoeckemann is already looking to the future. With accurate, continuous IOP monitoring, one can begin to imagine new sorts of closed-loop therapies, in which therapy is automatically adjusted to IOP readings or trends.

For the first time, says Stoeckemann, patients and clinicians will be able to see the curve of eye pressure measurements over a period of time so physicians can deliver better individualized therapy and slow down visual field progression. With Implandata's sensor, he says, "You can see the fluctuations and what happens when you change therapy. That gives all of us confidence that if you use the device you can detect undertreated or wrongly treated patients." From there, he imagines, Implandata will be able to generate data about how all of the drugs used in glaucoma impact disease.

Stoeckemann is already looking to the future. With accurate, continuous IOP monitoring, one can begin to imagine new sorts of closed-loop therapies, in which therapy is automatically adjusted to IOP readings or trends. For now, though, the company remains focused on getting through clinical trials, getting CE mark clearance, and getting its first-generation device into patients. Stoeckemann notes that so far, "preliminary data fulfills all the value propositions we attached to this product in the first place."