Abstract

Currently there is no portable device that can check diseases of the aging eye such as: *Glaucoma, age-related macular degeneration, Diabetic retinopathy, Alzheimer's Disease, Cataract, clinically significant macular edema, keratoconjunctivitis sicca (dry eye disorder), Sjogren's syndrome, retinal hard exudates, ocular hypertension, uveitis.*

We propose a portable device which when placed before one eye but without any physical contact, analyzes its natural infrared spectrum in order to detect molecules that reveal a potential medical condition. The device asks to the user to consult a medical doctor, with an indication about urgency but without disclosing any medical information. On contrary the doctor can securely access a wealth of information without needing a dedicated device.
The medical doctor proposes this tool to the patient, and operates it for the full life cycle. The medical doctor is constantly in control of the device and the relation she has with her patient.

The device is portable, costs less than $2000. We plan to conform to ISO 15197:2013.
A US provisional application for patent is considered for this device.

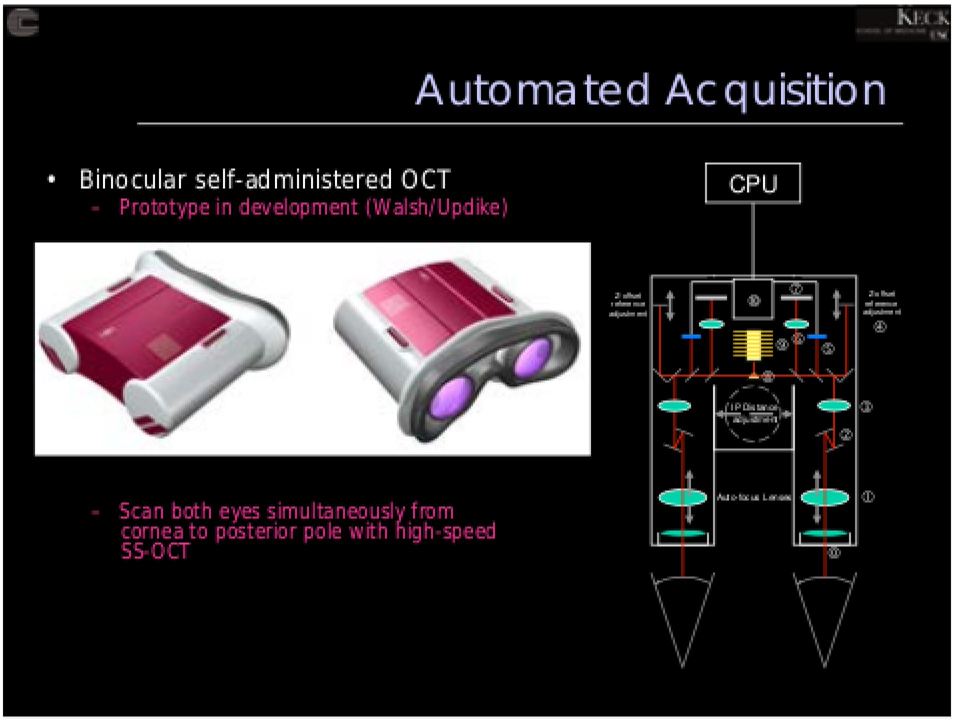
Description of new eye care device.

A whistle-blower, not a tool for medical diagnostic

This is a device which is used as a “eye health sentry”. It can check a wide range of eye diseases, but it is not a medical device (MD) in US (but it may be classified as a MD in EU), as it does not deliver any diagnostic.
What it does, is looking for certain molecules that are often associated with certain diseases. As this device is designed to be used by patients, it is not used in a controlled environment, so the molecule detection method may fail in some situations.
When it detects a possible illness it doesn't tell much information to the patient, only to undergo a medical check and meanwhile it gives a few recommendations to better manage the suspected illness.

An easy to use device

Contrary to other portable devices like Netra, it doesn't need user participation to the measuring act. It doesn't use fragile hardware, and has no contact with eye. It either doesn't use laser, ultrasounds or any other source of radiation or energy: It is non invasive.



Tailored for adult or aging people

While simply advising the user about the need to consult, it checks a far greater range of diseases than competition which often is limited to nearsightedness, farsightedness, and astigmatism which are obvious modifications of optical characteristics of the eye.
Currently there is no portable device that can check diseases like: *Glaucoma, age-related macular degeneration (AMD), Diabetic retinopathy (DR), Alzheimer’s Disease (AD), Cataract, clinically significant macular edema (CSME), keratoconjunctivitis sicca (KCS or dry eye disorder), Sjogren’s syndrome (SS), retinal hard exudates, ocular hypertension, uveitis.*

However if 'Eye's health sentry' can check for a collection of wildly occurring eye diseases it is not intended for genetic, obvious and rare eye diseases. Usage is for adult only.

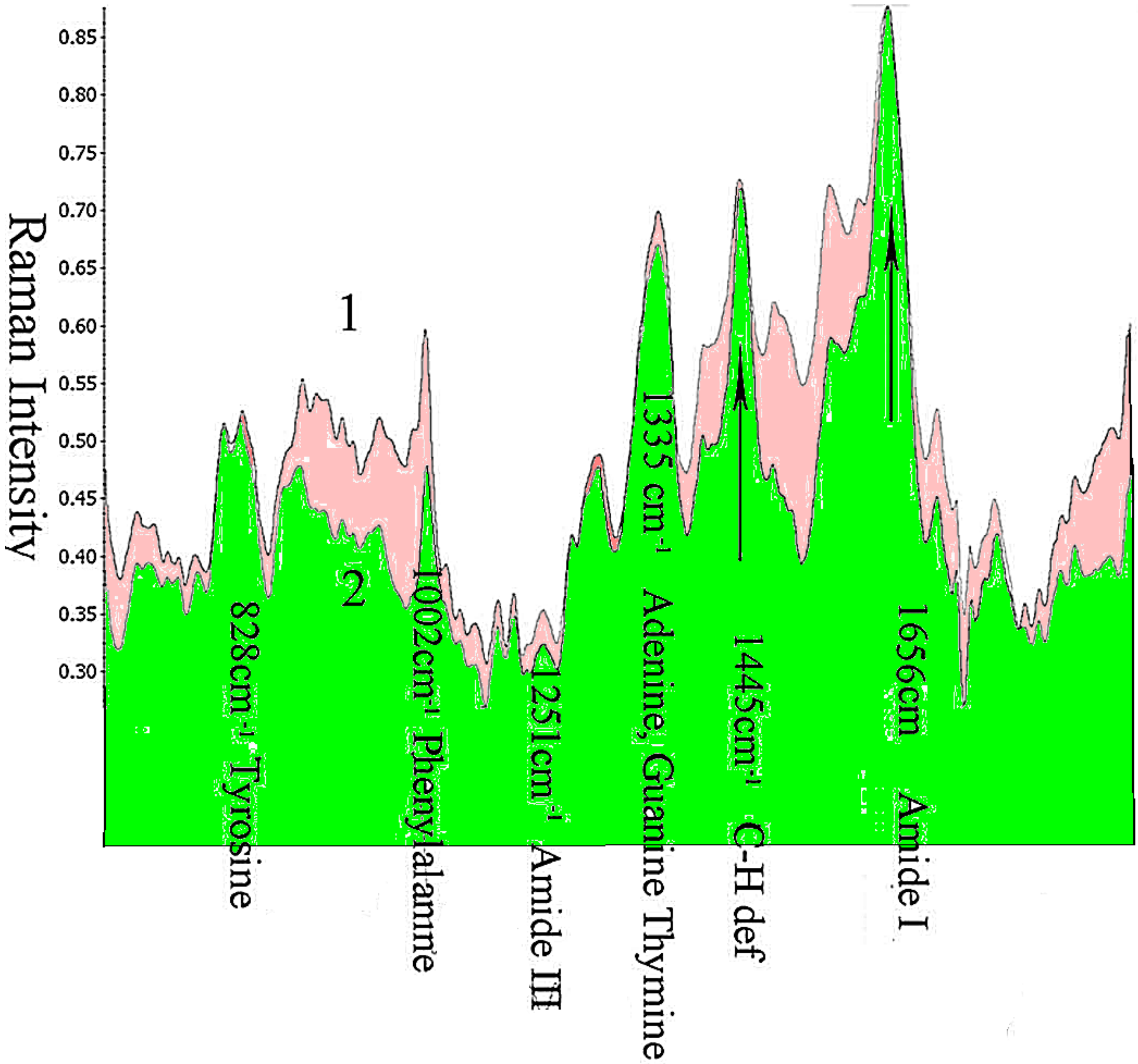
Use biomarkers as proxy for disease diagnostic

It works by searching for biological markers for a wide range of diseases in the eye. It is a non invasive check relying on spectroscopy.
A biomarker, or biological marker, generally refers to a measurable indicator of some biological state or condition. Biomarkers are often measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Biomarkers are used in many scientific fields.
A biomarker, or biological marker, is a surrogate measurement designed to characterize and quantify an underlying disease process. The perfect biomarker would be a substance that is easily quantifiable and easy to obtain without invasive procedures, allowing the possibility to follow the progress of the disease through multiple sampling over time.

Predictive biomarkers help to assess the most likely response to a particular treatment type, while prognostic markers shows the progression of disease with or without treatment. One example of a commonly used biomarker in medicine is prostate-specific antigen (PSA). This marker can be measured as a proxy of prostate size with rapid changes potentially indicating cancer.

Better than non invasive: Passive detection

This device doesn't use any laser, in fact it doesn't emit anything, it only gather the vast emission spectrum in the infrared that the human body irradiates naturally. It detects many spectrum rays in the thermal emission, performs statistical analysis and classify them as molecules by comparing spectra to a database.
Molecule identification eye's infrared spectrum is illustrated in the next picture which compares two dogs eyes, one healthy (in green) and the other with glaucoma [19] (in pink). It easy to see how the healthy eye spectrum is different from the one with a condition.
However this picture uses a different kind of spectroscopy than the one we propose (Raman vs thermal emission spectroscopy). This picture is here to illustrate spectroscopy usage in ocular disease detection, thermal emission spectroscopy is presented in detail in another section.



Raman Intensity
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
1
2
828cm-1 Tyrosine
1002cm-1 Phenylalanine
1251cm-1 Amide III
1335 cm-1 Adenine, Guanine Thymine
1445cm-1 C-H def
1656cm Amide I

Use case

The first time

There is a mandatory learning event at the doctor office, where the doctor makes an opthalmic assessment of patient. The device, operated by the doctor, learns patient's eye spectrum, and is initialized with the current patient health problems. The doctor may add other health information as well. The doctor accesses the device, on her own computer via Bluetooth. There is a dedicated software on doctor's computer that makes it possible to the doctor to manage the patient's device. The 'Eye's health sentry' is calibrated under the control of the doctor.
There is also a security pairing event which will make it possible for the 'Eye's health sentry' and the doctor's PC (or tablet) to dialog securely later (a shared secret is elaborated, for example with Diffie-Helman key exchange protocol.

At home

When at home, much later the patient may be willing to make an assessment of her eyes. She put the device in front of each eye. The device tells if it receives a correct spectrum, for example if the user still bore glasses it won't work as glass is partly opaque to infrared.
If the received spectrum is OK in overall, the device could be removed from eye's proximity and rests on a table, while it will analyze the spectrum for common biomarkers.
If a significant deviation from the learned state happens, the device informs the user verbally. A more precise report is available for patient's doctor, via Bluetooth.

At the doctor office, when a medical condition is suspected

At doctor's office there is the software that makes it possible for the doctor to interrogate 'Eye's health sentry'. There are Windows/iOS and Linux versions of this software. What the doctor's computer needs to communicate with the patient device is a Bluetooth interface, which most modern PC or tablet have. The 'Eye's health sentry' can present the information it has, when the biomarker was detected, the estimated level it has. What disease it is linked to, etc...

The inner working of 'Eye's health sentry' may change by using a cloud processing facility to vastly improve the speed of calculations at doctor's office, if she wants to investigate several scenarios.

Calibration event each year at the medical doctor office

The doctor may change informations in the 'Eye's health sentry'. This device is calibrated under the control of the doctor.
The doctor's software may also update the 'Eye's health sentry' software.

A non invasive design without excitation source?

Usually non invasive devices in biology (like glucose monitors) use either ultrasounds, infrared absorption or Raman spectroscopy, and there are many other obscure technologies.
If we deal with the eye it's out of question to use any excitation energy. Even with non invasive glucose monitors, the skin suffers from repetitive ultrasound or laser impacts. And eyes are much more sensitive than skin.

Thermal emission spectroscopy (TES)

This technology resembles infrared emission spectroscopy, it is also called passive spectroscopy. The human body constantly emits in infrared band. This is usually simply called body heat, but it's the result of many phenomenas. As a molecule receives energy in the form of body's heat, it re-emits this energy on a specific band, a bundle of infrared light waves (its spectrum) with specific wavelengths. As there are thousands different molecule types in any area of the body, usually it's a bit difficult to detect one specific molecular spectrum in the received infrared flow. That's why excitation based designs are usually preferred in biology.

Thermal emission spectroscopy is known since a long time but little used as its only rarely needed. It is a bit similar to high school experimentations where students look at the spectrum of a distant street light with a dispersive spectrometer, except it is done in infrared spectrum. It has been proposed for non invasive continuous glucose monitors [20] and it is used in spatial applications where it is important to know the chemical composition of inaccessible landscapes. For example the Thermal Emission Spectrometer (TES) is an instrument on board Mars Global Surveyor. The TES instrument uses the natural harmonic vibrations of the chemical bonds in materials to determine the composition of gases, liquids, and solids that are kilometers away, without probing them with a laser or any other excitation source.

It is used as well by the U.S. Environmental Protection Agency to monitor and map the downwind hazard of the chemical plumes from train car derailments, chemical plant fires, and explosions. The agency uses multi- and hyperspectral infrared sensors at emergency-response sites to detect, identify, and map the infrared spectral absorption and/or emission features of the chemical vapor [23].

TES and eye are perfect fits

Eye is one of rare biological objects where thermal emission spectroscopy is interesting. there is the need to have a good understanding of the medium which is emitting infrared light. This is why there is still no glucose monitor based on spectroscopy, as skin is a complex medium which irradiates on many infrared waves simultaneously.

But the eye is very different from skin, the fact it is transparent also means it emits little in visible or near infrared, it's also very homogeneous in chemical composition, while the skin is very heterogeneous, meaning a slight modification is easy to detect as a quite different spectrum (see last picture). In fact we are in an opposite situation to non invasive glucose monitors, their designers work very hard to remove the “radiation background”, and here we use it.

Opthalmology and chemical biomarkers

There are different kind and usage of biomarkers. A single biomarker may be ideal in clinical use but it hardly exists due to the fact that many diseases are multi-factorial diseases. One good example is from the dry eye study carried out in Singapore eye research institute [1]. One of the best single tear chemical biomarker may differentiate patients with or without dry eye with 80% accuracy. However, a combination of four tear chemical biomarker (biomarker panel) can significantly increase the diagnostic accuracy to 95% [1].
In our case we are only interested in biomarkers that are proteins and that have a significant activity in the so called mid infrared fingerprint domain. This is because we do infrared emission spectroscopy.

Disease	Biomarkers	Article
myopia (near-sightedness),	Transthyretin 25-hydroxyvitamin D	[18] [21]
Glaucoma	amide III, adenine, guanine, thymine	[18]
keratoconjunctivitis sicca (KCS or dry eye disorder)	Matrix metalloproteinase 9	[22]
Sjogren’s syndrome (SS) is a severe form of keratoconjunctivitis sicca	lactoferrin (Lf)	[3]
age-related macular degeneration (AMD)	Conflicting data exist regarding a possible link between C-reactive protein (CRP), a marker of non-specific inflammation, and AMD, as well as interleukin-6 (IL-6). Some researchers suggest that CRP may have a direct role in AMD development through its ability to induce complement activation, with another group describing a link between elevated CRP levels and AMD progression.	[4][5]
AMD	Seddon's group described an association between IL-6 and AMD progression, yet Klein et al. found no such association.	[5] -[6]
Diabetic retinopathy (DR)	In a cohort of the Diabetes Control and Complications Trial, the severity of retinopathy was associated with increasing triglyceride levels and inversely correlated with HDL levels.	[8]
DR	Some authors have suggested that serum apolipoprotein levels may be stronger biomarkers of DR than traditional lipid measures, such as total cholesterol, LDL or HDL cholesterol, or even the LDL-to-HDL ratio. The proteins apoAI (found in HDL) and apoB (found in LDL), and specifically the apoB-to-apoAI ratio, were significantly and independently associated with diabetic retinopathy development and severity.	[9]

DR	Studies suggest a significant association between the plasma plasmin-α2-antiplasmin complex and severity of DR.	[10]
Alzheimer's Disease (AD)	Whatever the role of Aβ in the healthy body, a large number of in vitro and in vivo AD studies, have shown that higher than normal Aβ levels cause oxidative stress in the brain. The eye is the only place in the body where vasculature or neural tissue is available for non-invasive optical imaging . The Aβ protein involved in the pathogenesis of AD in the brain has also been found to exist in the lens (Aβ40 and Aβ42), aqueous humor (Aβ40) and vitreous humor (Aβ42) of the normal human eye .	[12-13][11]
Cataract	pentosidine and imidazolone	[14]
clinically significant macular edema (CSME)	high-sensitivity C-reactive protein (hsCRP)	[2]
retinal hard exudates	high-sensitivity C-reactive protein (hsCRP)	[2]
retinal hard exudates	intercellular adhesion molecule 1 (ICAM-1)	[2]
ocular hypertension	Rise in lactate in vitreous humor	[15] [16]
uveitis	Rise in lactate in vitreous humor	[17]

Is it classified as a medical device?

It is important to know if 'Eye's health sentry' is a medical device or not because in this case it is mandatory to support specific regulations and development costs are higher. In US our interpretation is that it will not be classified as a medical device, essentially because it does no diagnosis. In EU our interpretation is that it is a medical device, because its usage is for monitoring and disease prevention. However the EU mandates less obligations, and they could be fulfilled with EN 62304 and ISO 15197:2013. The later standard is also recognized by FDA for glucose monitors.

In USA

The FDA definition of a mobile medical application is as follows:

> *a "mobile medical app" is a mobile app that meets the definition of "device"*
> *in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act);*
> *and either:*
> *— is used as an accessory to a regulated medical device; or*
> *— transforms a mobile platform into a regulated medical device.*

The following are not medical devices, the second item describes well 'Eye's health sentry':

- Mobile apps that are electronic "copies" of medical textbooks, teaching aids or reference materials, or are solely used to provide clinicians with training or reinforce training previously received.
- *Mobile apps that are solely used to log, record, track, evaluate, or make decisions or suggestions related to developing or maintaining general health and wellness*
- Mobile apps that only automate general office operations with functionalities that include billing, inventory, appointments, or insurance transactions.
- Mobile apps that are generic aids that assist users but are not commercially marketed for a specific medical indication.
- Mobile apps that perform the functionality of an electronic health record system or personal health record system.

In EU

The Medical Device Directive 93/42/EEC (MDD) 8 is the primary source of regulation governing health apps across European member states. Under clause 2(a), a medical device is defined as follows:

> *any instrument, apparatus, appliance, software, material or other article,*
> *whether used alone or in combination, including the software intended by*
> *its manufacturer to be used specifically for diagnostic and/or therapeutic*
> *purposes and necessary for its proper application, intended by the*
> *manufacturer to be used for human beings for the purpose of:*
> *— diagnosis, **prevention, monitoring**, treatment or alleviation of disease,*
> *— diagnosis, monitoring, treatment, alleviation of or compensation for an*
> *injury or handicap,*
> *— investigation, replacement or modification of the anatomy or of a physiological process,*
> *— control of conception,*

Rationale as to why the innovation is needed or would be beneficial to patients

Here are six reasons why this device is very important for patients and their doctors:

- Aging people are used to discover one morning that something they assumed working flawlessly in their body, becomes dysfunctional for ever. Most often it's small things but that creates an insecure atmosphere. Devices that give health information, even if it's simply a call to visit the doctor, are reassuring because the patient is again able to gain some control on her body.

- Sometimes for people or healthcare workers, it's not clear if some medical condition is only some temporary problem that will quickly and easily disappear without any treatment, or if it is something that needs a doctor examination.

- Health insurance also might recommend such device because it may help to manage very early conditions that might otherwise evolve in costly complications.

- Another aspect is that the diseases 'Eye's health sentry' detects may evolve very quickly, in a matter of weeks. It's impossible to check every few days in a laboratory, all people who may develop one of those conditions. 'Eye's health sentry' can make it possible.

- Most of the medical conditions that are detected with 'Eye's health sentry', are usually very hard to discriminate from each other. 'Eye's health sentry' tells to the doctor which biomarker was detected, so risks of confusing one illness with another are reduced.

- It can detect the build-up of a biomarker, while the disease is still manageable and hopefully reversible.

Description of how the proposed service would encourage patients to visit eye care professionals

'Eye's health sentry', doesn't give much information to the user, but it tells her two things:

- She may need to consult her medical doctor
- The level of urgency of this visit.

'Eye's health sentry' may also be perceived as an independent, “fair” source of information that it is worth to have. It doesn't advocate treatments, it just tells one very important information that users seek but most of the time, never acquire in a satisfactory manner, it's sometime too early, often too late: *Is it time to consult?*

'Eye's health sentry'

The 'Eye's health sentry' is a little device that the user put in front of her eye to analyze it. A led tells the user if the device is correctly positioned in front of the eye. It is achieved with eyebrow software recognition.

Requirements

This list of requirements is based on lessons learn while studying other medical devices development.

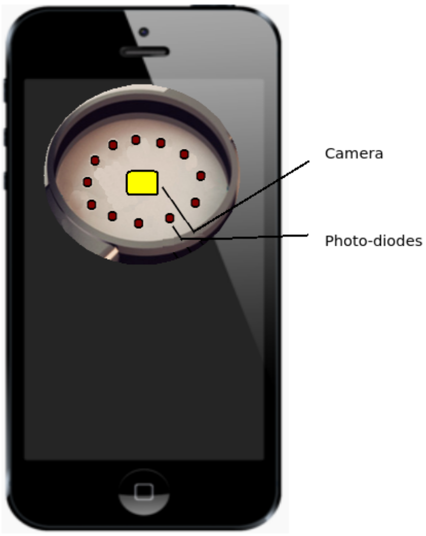
Requirement	Our response
RQ1: Performance characteristics of the device, clinical efficacy and reproducibility of measurements.	We do not assume there is a simple solution. - We use a large number of spectrum peaks. - Sensors are used to gain contextual information (eye's position, dryness, temperature and ambient temperature)
RQ 2: It should not irritate eye.	Our device is completely passive and don't even requires contact
RQ 3: It should have little calibration time	- We aim at a calibration event each year at the medical doctor office
RQ 4: Little lag time between measurements.	This is mainly limited by the mathematical processing time (PCA, PLS, etc..) that's why our device is powered by the grid when used at the doctor's office to make it possible to use power hungry CPU.
RQ 5: It should support rapid temperature changes (for example, going into an air-conditioned building after being outside on a hot day).	Eye's and ambient temperature, as well as violent variations will be managed for example by adjusting the spectrum analysis software parameters.
RQ 6: It must not be sensitive to sunlight.	Actually a sensor will tell the user that measurements must be done in a different environment, such as toilets.
RQ 7: Measurement should be stable enough to be continuously used for weeks or months.	On contrary to some GCMs that use a blood glucose model, where a common molecule is measured in skin and used as a proxy to know glucose in veins, and this model becoming slowly obsolete as body changes, the eye do not mandate an "eye model" as the eye is quite homogeneous.

RQ 8: It should have no variability from user to user, and even on the same user at different time. Performance should not be affected by variables as innocuous as skin color, excessive perspiration.	That the reason we mine the “background noise” to understand the body inner working. In addition sensors are used to make sure the case rest on the skin, the temperature is normal, the skin is dry, etc...
RQ 9: It can read results verbally for visually-impaired or blind people as blindness or vision problems are very common for diabetes patients.	'Eye's health sentry' does it.
RQ10: In order to remove adoption barriers for new technology, an 'Eye's health sentry' device should be ordered only by a physician.	Medical doctors should evaluate barriers (physical abilities, mental status, insurance coverage, etc.) and not have to support something they are not ready for.
RQ11: Cost of the device. Even at $2,000, without a substantial reimbursement level, it is a huge cost for many users.	We will aim at a similar price at least for a first generation, the device will have an operational life of 5 years. Later devices may have a much lower cost.
RQ14: Health products that are new to the market require a sizable sales force to educate health-care professionals and end user, and to create product awareness in various marketing channels.	This sizable sales force must be trained to educate health-care professionals and end users.

The liaison between medical doctor's computer and 'Eye's health sentry' is done in BlueTooth. We will use the existing health bluetooth profile. Secure connections are required in order to make it impossible for this connection to be spied or otherwise hacked.

'Eye's health sentry' process the spectrum received from the eye with statistical tools like principal component analysis (PCA) which returns a number of “components”, each one being a molecule which has emitted an infrared spectrum. Those molecules could be glucose, urea, cholesterol, triglyceride, albumin, hemoglobin, as well as hematocrit. Those “components” are then processed in a skin blood model which will predict the glucose amount.

'Eye's health sentry' has several main components, the photo-diodes, sensors and a SoC (an integrated computer in a single chip).



In the picture above, the lid with the infrared windows, is removed and we can see the photo-diodes that process infrared light coming from the eye. This hardware could be installed in boxes with a different form factor as it is self-contained.

The camera is used for eye position adjustment and detection of certain conditions.
The photo-diodes are used for spectrum measurement. This disposition in circle is for illustration only, a more compact design may be used later.

We use internal baffles around the photo-diodes to mitigate stray lights. The photo-diodes are directional, they only detect infrared coming through the infrared band-pass window.

Humidity and temperature sensors

A set of simple sensors verify that the optical path corresponds to the one designed for the 'Eye's health sentry' usage. If this is untrue, a message asks the user to correct the situation, for example by improving the contact of the 'Eye's health sentry' case with the eye, by making the eye dry, etc...
SMC temperature sensing chips such as the AD592 by Analog Devices as well as standard thermistors for ambient temperature measurements can be used. SMC humidity sensors such as the HIH-3602 can be used. This is instrumental in overcoming one of the main roadblock of non invasive heath monitoring devices which sometimes provide unreliable answers. In those situations our device tells its user that it can't provide any answer, and it provides tips how to solve the problem.

Thermal infrared spectrometer

Fourteen photo-diodes are used to obtain the spectra of the detected light from the sample. 14 wavelengths are measured, instead of the four usual measurements.
Semiconductors detectors are used to accurately count the number of photons at each wavelength. However semiconductors characteristics have a lot of variability, this should be taken in account in risk management. Ordinary photo-diodes have also a too wide detection spectrum to be good filters. Special measures must be taken to make precise measurements. We have a proprietary low cost technology that makes it possible to obtain relatively selective measurements from each diode.

Advanced algorithms are used to analyze the spectrum. They take in account eye's and ambient temperatures. The background information is used for correcting the measurements.

Software

Importance of “Background noise”

One remark could be made: Most non-invasive proposals based on spectroscopy try to eliminate the “background noise” by using different mathematical technologies. However it seems a bad idea.
The “background noise” is full of information about the eye composition and body as a system. The relative level of eye's molecules is important for making accurate measurements. It's not enough to detect a presence of a molecule, it's relative amplitude must be cross-checked with other molecules, because some situations may look some situation as anomalous when it's only not an average situation. Many failures in commercialization of glucose CGM have their root cause in the failure to see that many perfectly normal situations cause anomalous measurements for example dehydration, or pregnancy.

Other interfering conditions

- Altitude, temperature, and humidity. We should test those with appropriate sensors.
- Improper storage and handling, eye unclean, unclean case. The device should incorporate some “watch dog” mechanism to stop measurements when they may become inaccurate and signal this to the user, and maybe to a third party such as a doctor or insurance.
- Improper case location on relative to eye's.

Features implemented in the 'Eye's health sentry' for medical doctors:

An average eye monitor would only provides a "snapshot" at a single moment in time. Our device, though, must give the user a better view of her eye health trends. It provides users with:

- A graphic and informative log of past 48 hours only available to medical doctors.
- The direction the condition is evolving and if there is need to consult a doctor.
- Early notification of other health problems, by looking at several other molecules concentration like diabetes.
- Insights into how food, physical activity, medication, and illness impact health problem.
- Valuable information at crucial points during the day, including before and during exercise, prior to driving, before test/exam-taking.
- Interface to insurance.

Conclusion

We have presented 'Eye's health sentry', a device that relieves from angst of “when to consult, is it already too late?” for frightening eye's diseases, that are common in aging people.
It is designed to be used by anyone. There is no special handling requirement.
No similar device exists in the consumer market, but at the same time it is not a universal tool. It fits the segment of monitors of certain ocular diseases by looking at proxy signs, without any contact. It offers no diagnostic. There is the mandatory need of a medical doctor in order to diagnose and propose a treatment.
'Eye's health sentry' is not a complicated nor a costly device. If produced in large numbers, the cost could dramatically drop.

Does it help fully enjoy all the possibilities of life?	Yes, it enables to detect and manage heath threats that would damage patient's quality of life.
Does it allows an eye care professional to identify serious underlying health concerns?	Yes, it is mandatory as it may detect signs of very serious diseases.
Is the focus being placed on preventative care?	Yes, it detects the build-up of a biomarker, while the disease is still manageable.
Does it encourage to seek regular, ongoing care from vision professionals?	Yes, its designed to mandates regular visits to health professionals (see use case section).
Does it demonstrates to patients the value of an ongoing relationship with their eye care professionals.	Yes because only the doctor diagnoses the illness and proposes a treatment.
How can eye care professionals be better positioned to help patients with their own concern?	Our device makes it possible to differentiate between diseases that have similar symptoms by may have dramatically different outcome.
Does it enables additional services to be offered by eye care professionals?	Managing our device is a additional service. We are open to make it possible more personalization of the device by the medical doctors.
Why the innovation is needed or would be beneficial to patients?	No similar health devices exist even if it deals with diseases that are life changing threat.

References to literature or other studies in support of submission

[1] Zhou L, Beuerman RW, Chan CM, Zhao SZ, Li XR, Yang H, Tong L, Liu SP, Stern ME, Tan DTH. Identification of Tear Fluid Biomarkers in
Dry Eye Syndrome Using iTRAQ Quantitative Proteomics. Journal of Proteome Research, 2009, 8(11), 4889-4905.

[2] Prospective Study of Inflammatory Biomarkers and Risk of Diabetic Retinopathy in the Diabetes Control and Complications
Rajeev H. Muni, MD, MSc, FRCSC; Radha P. Kohly, MD, PhD, FRCSC; Eudocia Q. Lee, MD, MPH; JoAnn E. Manson, MD, DrPH; Richard D. Semba, MD, MPH; Debra A. Schaumberg, ScD, OD, MPH
Epidemiology April 2013

[3] Abnormal protein profiles in tears with dry eye syndrome.
Ohashi Y, Ishida R, Kojima T et al.:
American Journal of
Ophthalmology 136(2), 291-299 (2003).

[4] Seddon JM, George S, Rosner B. Progression of age-related macular degeneration: Prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. Arch Ophthalmol. 2005;123:774-782.

[5] Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration.
JAMA. 2004;291: 704-710.

[6] Klein R, Klein BE, Knudtson MD, Wong TY, Shankar A, Tsai MY. Systemic markers of inflammation, endothelial dysfunction, and age-related maculopathy.
Am J Ophthalmol. 2005;140:35-44.

[7] Tsai DC, Charng MJ, Lee FL, Hsu WM, Chen SJ. Different plasma levels of vascular endothelial growth factor and nitric oxide between patients with choroidal and retinal neovascularization.
Ophthalmologica. 2006;220:246-251.

[8] Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort.
Lyons TJ, Jenkins AJ, Zheng D, et al.
Invest Ophthalmol Vis Sci. 2004;45:910-918.

[9] Apolipoproteins and diabetic retinopathy.
41. Chait A, Montes VN.
Diabetes Care. 2011;34:529-531.

[10] Inflammatory, hemostatic, and other novel biomarkers for diabetic retinopathy: the

multi-ethnic study of atherosclerosis.
Nguyen TT, Alibrahim E, Islam FM, et al.
Diabetes Care. 2009;32:1704-1709.

[11] Ocular Biomarkers for Early Detection of Alzheimer’s Disease
Shaun Frost, Ralph N Martins, Yogesan Kanagasingam

[12] Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease.
Goldstein LE, Muffat JA, Cherny RA, Moir RD, Ericsson MH, Huang X, Mavros C, Coccia JA, Faget KY, Fitch KA, Masters CL, Tanzi RE, Chylack LT, Jr., Bush AI (2003)
Lancet 361, 1258-1265.

[13] Vitreous fluid levels of beta-amyloid((1-42)) and tau in patients with retinal diseases.
Yoneda S, Hara H, Hirata A, Fukushima M, Inomata Y, Tanihara H (2005)
Jpn J Ophthalmol 49, 12-108.

[14] Increased level of advanced glycation end products in human catractous lenses.
Franke S, Dawczynski J, Strobel J, Niwa T, Stahl P, Stein G
J Catract Refract Surg 2003, 29:998-1004.

[15] Longitudinal non-invasive proton NMR spectroscopy measurement of vitreous lactate in a rabbit model of ocular hypertension.
Ngumah QC, Buchthal SD, Dacheux RF.
Exp Eye Res. 2006; 83:390-400.

[16] Rucker JC, Biousse V, Mao H, Sandbach J, Constantinidis I, Newman NJ. Detection of lactate in the human vitreous body using proton magnetic resonance spectroscopy. Arch Ophthalmol. 2003; 121:909-11.

[17] Metabolomic analysis of human vitreous humor differentiates ocular inflammatory disease
Stephen P. Young, Maged Nessim, Francesco Falciani, Victor Trevino, Somnath P. Banerjee, Robert A.H. Scott, Philip I. Murray, Graham R. Wallace
Molecular Vision 2009; 15:1210-1217

[18] Vitreous and serum levels of transthyretin (TTR) in high myopia patients are correlated with ocular pathologies.
Jun Shao, Yu Xin, Rongxiu Li, Ying Fan
Clinical biochemistry03/2011; 44(8-9):681-5

[19] Exploring Raman spectroscopy for the evaluation of glaucomatous retinal changes
Qi Wang, Sinisa D. Grozdanic, Matthew M. Harper, Nicolas Hamouche, elga Kecova, Tatjana Lazic, and Chenxu Yu
Journal of Biomedical Optics 16(10), 13006 (October 2011)

[20] A Novel Noninvasive Blood Glucose Monitor
Carl D. Malchoff , Kamal S Houkri , Julian I. Landau , Janusz M. Buchert
Diabetes Care 25:2268 –2275, 2002

[21] Myopia is associated with lower vitamin D status in young adults.

Yazar S, Hewitt AW, Black LJ, McKnight CM, Mountain JA, Sherwin JC, Oddy WH, Coroneo MT, Lucas RM, Mackey DA.
Invest Ophthalmol Vis Sci. 2014 Jun 26;55(7):4552-9. doi: 10.1167/iovs.14-14589.

[22] Sensitivity and specificity of a point-of-care matrix metalloproteinase 9 immunoassay for diagnosing inflammation related to dry eye.
Sambursky R, Davitt WF 3rd, Latkany R, Tauber S, Starr C, Friedberg M, Dirks MS, McDonald M.
JAMA Ophthalmol. 2013 Jan;131(1):24-8. doi: 10.1001/jamaophthalmol.2013.561.

[23] Emergency response chemical detection using passive infrared spectroscopy

Robert Kroutil, Paul Lewis, Mark Thomas, Timothy Curry, David Miller, Roger Combs, Alan Cummings

SPIE Newsroom. DOI: 10.1117/2.1200604.0157

Table des matières