ISSUE - 6 | Spring 2021

LASER AND ULTRASOUND CO-ANALYZER FOR THYROID NODULES

NEWSLETTER

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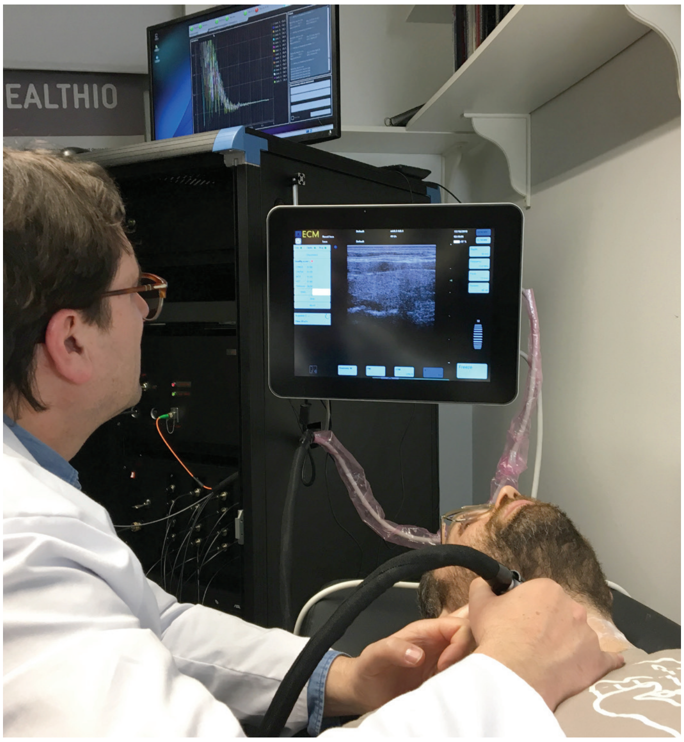
A study in *Biomedical Optics Express* by the LUCA consortium reports on several study cases and clinical tests conducted to validate the accuracy and high quality of measurements achieved by the LUCA device



Description: first lab tests in 2019 of the LUCA device at ICFO research center in Barcelona. Dr. Mattia Squarcia tests the probe on a healthy patient to see the performance of the measurements.

Thyroid nodules are a common pathology having a prevalence of 19-76% when screened with ultrasound, with higher frequencies in women. Current medical methods used to assess the malignancy of a nodule consist in performing an ultrasound, followed by a Doppler ultrasound, and then a biopsy. However, unfortunately, these methods present both low specificity and low sensitivity. This insufficient effectiveness in accurately being able to diagnose thyroid tumors leads to many unclear or unnoticed cases as well as many others that undergo unnecessary surgeries (false positives) and increase the cost of medical healthcare, not to mention the reduction of quality of life of patients.

The **EU-funded project Laser and Ultrasound Co-analyzer for Thyroid Nodules (LUCA)** started in 2016 and over its 5 years of duration, it worked on the development of a new low-cost near-infrared optical device combined with ultrasound that searched to provide doctors with enhanced information required to provide better and more specific results in thyroid nodule screening. The goal of such device was mainly to enable a better diagnosis of this type of cancer because so far, there was no accurate way of determining whether a thyroid tumor as benign or malignant.

The LUCA device is a **multi-modal platform** combining near infrared light, **time resolved spectroscopy (TRS)**, **diffuse correlation spectroscopy (DCS)**, and **ultrasound** in one single device.

Clinical testing with LUCA

The study recently published in Biomedical Optics Express and authored by members of the consortium reports on several study cases and clinical tests conducted to validate the accuracy and high quality of measurements achieved by the LUCA device.

As a first step, the TRS and DCS modules were tested

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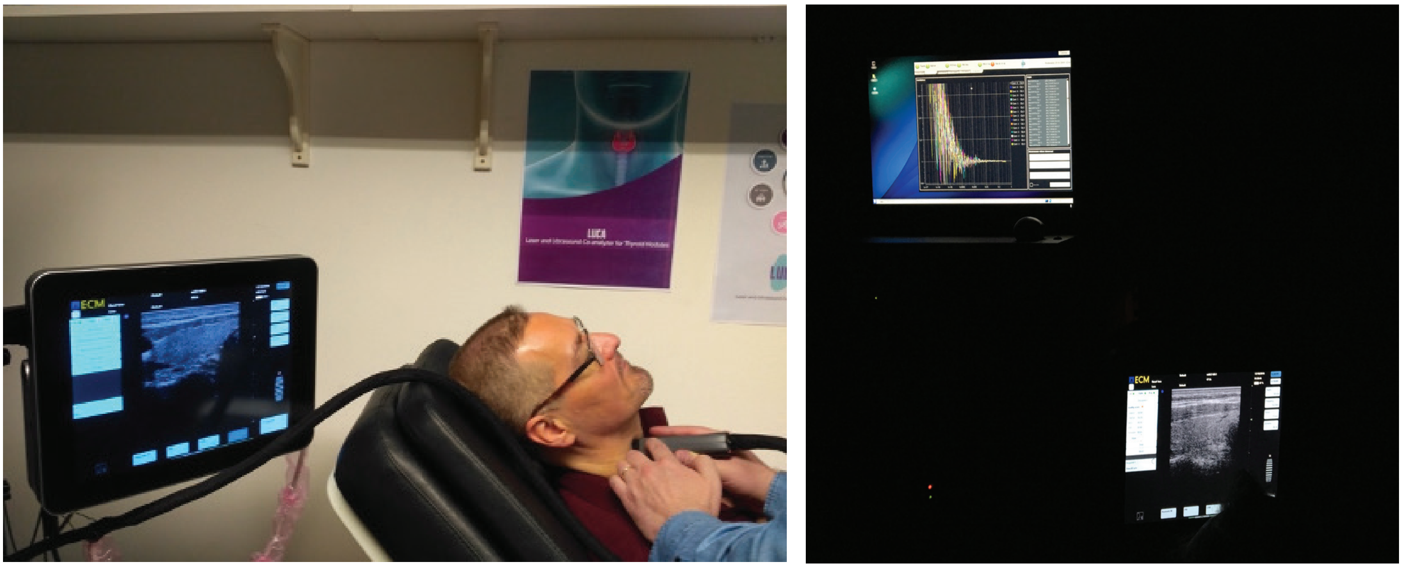


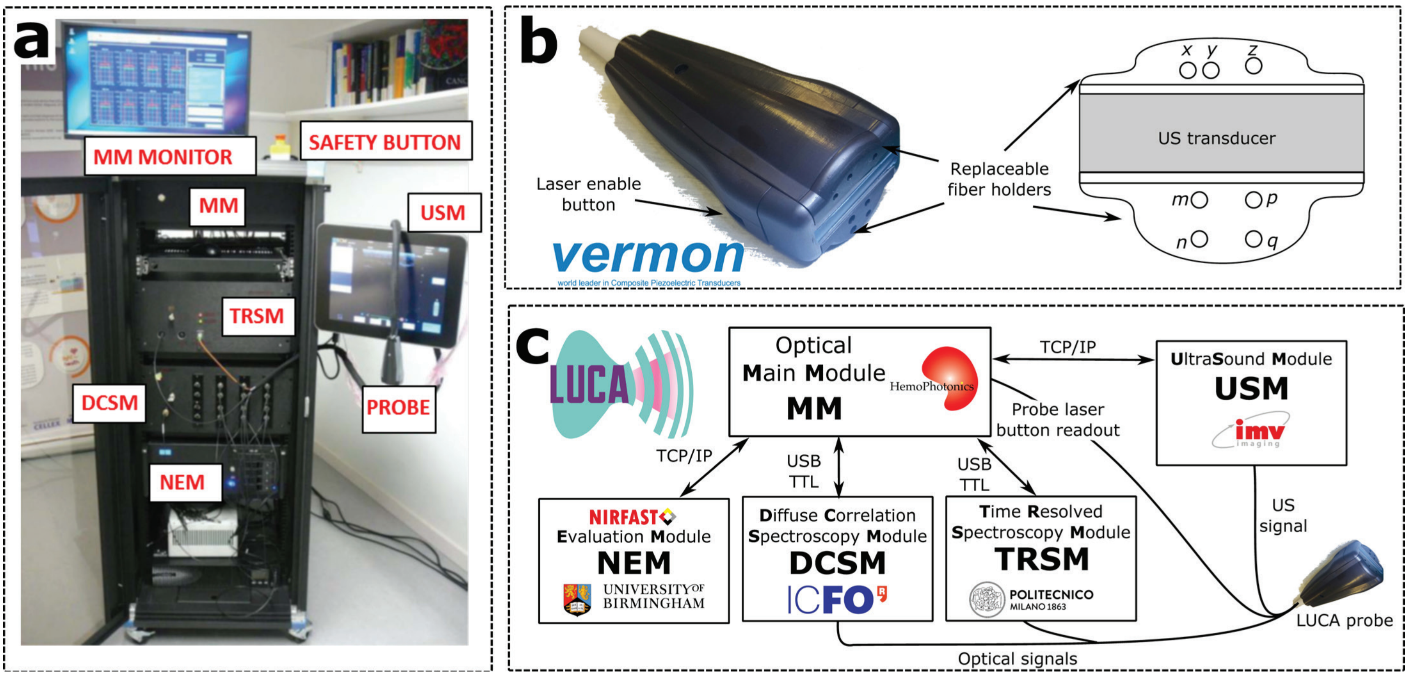
Description: first lab tests in 2019 of the LUCA device at ICFO research center in Barcelona. Dr. Mattia Squarcia tests the probe on a healthy patient to see the performance of the measurements.

independently using phantom 1 tests to validate the performance of both under the different European medical standardization protocols. For the former module, a set of solid phantoms with different absorptions and scatterings was used to assess the capability of the device to detect absorption and scattering changes, while for the latter, a set of liquid phantoms with different viscosities was used to assess the capability of the device of measuring the movement of the particles in suspension in the liquid phantom. The tests performed did prove to be successful, validating the outstanding performances of both modules.

Then, as a second step, the team of experts performed a series of in vivo characterization tests on a model healthy patient. By scanning the thyroid gland, simultaneously with ultrasound imaging, TRS and DCS, several times a day on different days and in different weeks, they were able to determine the precision of the LUCA device in measuring the hemodynamic parameters related to the thyroid gland.

Recently, the device has been moved into the clinical environment and tested on **18 healthy volunteers** and **47 patients** were diagnosed with **thyroid nodules** and were scheduled for thyroidectomy. The LUCA device showed potential for identifying the group of nodules as benign or malignant, which were stipulated as unclear cases with the classical ultrasound screening technique. By analyzing the metabolic rate of **oxygen consumption** and **total hemoglobin concentration**, the device was able to classify **thirteen benign and four malignant nodules** with a **sensitivity of 100% and specificity of 77%**.

Dr. Mireia Mora from the August Pi i Sunyer Biomedical



Description: Photo of the LUCA device with all the components (a), the head of the probe (b) used for scanning the thyroid, and the specific component developed by each of the consortium members.

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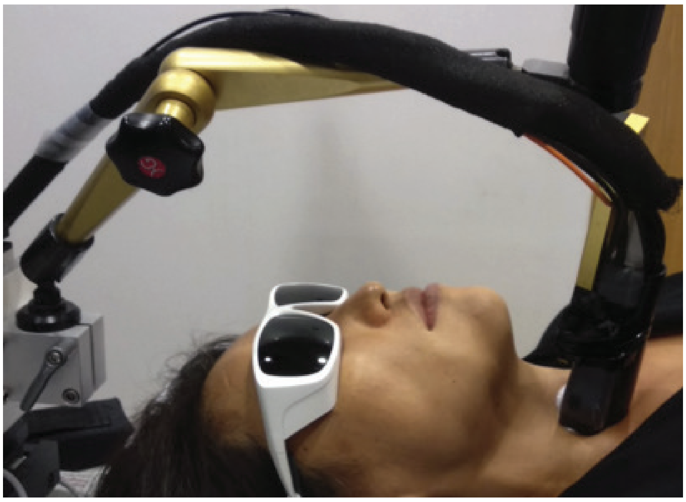


Description: Set up for thyroid repeatability measurements of the in vivo characterization tests with a healthy patient.

Research Institute (IDIBAPS) in Barcelona, Spain, which is responsible for the clinical application of the tool, under the direction of Prof. Ramon Gomis, highlights the fact that "*The need to improve the current standards of thyroid cancer diagnosis has driven us to participate in this multidisciplinary project. We have taken the first steps in preclinical testing, but are sure that with this technology we will be able to avoid unnecessary surgeries and thus improve the quality of life of our patients*".

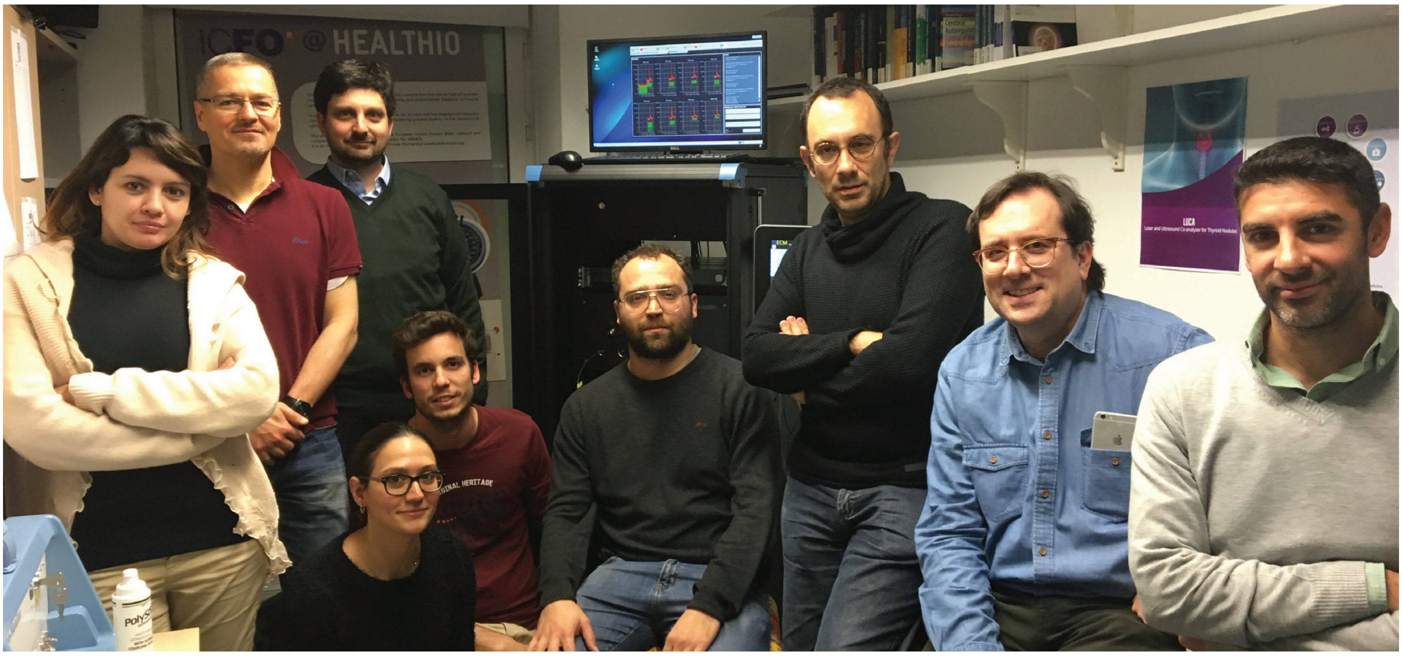
Dr. Turgut Durduran, coordinator of the LUCA project, group leader at ICFO of the Medical Optics research group, commented that "*this project has allowed us to develop a unique optical-ultrasound platform that we are confident that will find a use in the clinical thyroid cancer screening*". Recent advances of diffuse optical techniques have shown that not only these techniques have a tremendous potential in this field, but other fields as well, such as breast, head and neck cancer, abdominal cancer screening and therapy monitoring, cerebrovascular accidents (ictus) or even for **COVID19**, to name a few. Durduran finally remarks, "*We have learnt a lot and are anxious to continue working in this line of research because we believe that this technique could substantially improve the quality of measurements, narrow down diagnosis and helps asses in possible treatments of patients*".

Diffuse optics to improve medical diagnosis and treatment

Near infrared diffuse optical spectroscopy is an optical method that provides significant complementary information to other medical techniques used for imaging, such as ultrasounds. The LUCA device incorporates two different diffuse optical spectroscopy technologies (TRS and DCS) to improve the screening of thyroid nodules for cancer. These techniques have made it a completely novel device, because it is non-invasive and safe to use, portable, low cost, it probes deep enough into the tissue (>1cm deep) to give substantial information about the surrounding tissue, in this case the thyroid. In addition, it provides a real-time monitoring evaluation together with the ultrasound counterpart.

The TRS and DCS modules consist of custom-made components, such as laser heads and off-the-shelf-electronics for detectors and acquisition electronics, which makes them cheaper than any other commercially available TRS and DCS devices.

Despite being low cost, the custom developed components enhance performance features allowing the LUCA device to obtain high quality measurements of the tissue's hemodynamics (blood flow and oxygen at the microvascular level), chemical constitution (water and lipids concentration) as well as anatomy. ■



Description: Group picture of members of the LUCA consortium during the first tests of the LUCA device. From left to right, Gloria Aranda, Udo Weigel, Marta Zanoletti, Davide Contini (behind), Ferran José Torra, Lorenzo Cortese, Turgut Durduran, Mattia Squarcia, Giuseppe Lo Presti.

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A chat with Turgut Durduran on the end of the LUCA project

"We wanted to develop a new device for thyroid cancer screening which integrates optics and ultrasound, without significantly altering the current clinical protocols"

What are your general views about the final LUCA device and the process it took to reach this goal? Are you happy with the results?

The LUCA device is very unique. Even though different groups, including us, have introduced the concepts of combining these methods with ultrasound years ago, it has never been put together in such a thorough clinical instrument. Overall, the impression is really good.

What are the next steps that you envision for the device? Are you already planning to market the device?

It took a lot of hard work getting to this point! Being a unique device, we needed to develop new components, new modules while answering many questions about the new clinical problem we are tacking. It is not yet a device that is sold, but this was not the plan of the LUCA project during this phase anyway. We wanted to develop the components and subsystems that could be used for exploitation and to do pilot clinical studies.

The whole concept will now be evaluated for achieving an industrial device. We will continue to acquire data at the clinic, while testing it for other types of cancers and applications. At the same time, the involved industrial partners will look at redesigning the device. Hopefully in 5 to 6 years we will have commercial device that is approved as a medical device. Now that we have his platform, we are talking about new applications and are ready to test them with anyone interested.

You said you are currently testing it for other cancers. Are you also considering other illnesses?

Right now, the protocols we are starting are for other cancers and also for different cancer treatments, to monitor their efficacy. But we are also thinking about testing it for other purposes, such as looking at baby brain through the fontanel.

Do you plan to scale the clinical trials nationally and internationally?

So, we are discussing whether we have enough data to devise a multicenter clinical trial or not, which questions we should ask, and if we should use this device or the one already industrialized. Depending on all these aspects, we will decide.

What were the most difficult challenges and how did you overcome them?

The biggest challenge for us was to get all these different technologies to work together. We knew how to perform optics and how to do ultrasound, but we needed to integrate them. There were unexpected challenges, for example the gel you use when you perform an ultrasound turned out to be a major problem to tackle. Why? Because here we use the ultrasound to find where the nodules are while the clinicians are following their standard screening procedures. Once they find a nodule of interest, they take the optical data. So the effect of the gel had to be overcome. In our previous studies, we had seen that we had to put the ultrasound, find the location, paint a dot, clean it, and then do the optical measurement so it was not the same problem. Now, we wanted to do it altogether, developing a system that does not change the clinical protocols too much. It was an odd problem, but we had to solve it. We had to make sure the gel did not affect our light; we even invented new types of gel that allowed light to pass through them better.

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When working with clinicians, is there any time that they bring up other issues or problems they have to face in their daily practice?

Yes, absolutely! LUCA is a prime example of that. I was invited to speak at the endocrinology department at Hospital Clinic Barcelona, and I gave a talk about the effect of diabetes on the vasculature of the muscles, showing examples of brain monitoring and brain cancer. I was naive. When I finished my talk, Dr. Mireia Porta approached me and asked; "would it work on a thyroid?" At that time, we were doing studies on patients undergoing surgery at the same hospital and we had a device there, so we did some preliminary measurements with Mireia and her colleagues. That led to the writing of the LUCA project proposal. And during this project, many ideas did come up.. That is why having this device is so important, because it makes it a lot easier to follow our new ideas.■

LUCA Symposium on Synergy of light & sound for disease screening and therapy monitoring

Virtual Online Conference- November 5 & 12 - 2020

In November 2020, the LUCA consortium organised two events: a public event targeted to the general audience, and a closed panel discussion event targeted to specialized audiences, with the participation of relevant stakeholders from end-user and research communities.

Due to the COVID-19 pandemic situation, the conference was held in an online format and was organized in two sessions. On **November 5, 2020**, the consortium organized a public webinar entitled "**Synergy of light & sound for disease screening and therapy monitoring: Update on technology and clinical studies with diffuse optics and ultrasound**". A week later, on **November 12, 2020**, a closed panel discussion with expert speakers was held and relevant stakeholders were invited to participate and learn about the technology developed in LUCA and how it could assess clinicians in thyroid cancer screening.

The project results were presented, enriching discussions among panellists and audiences for clinical translation of the LUCA device as well as new opportunities for multi-modal imaging tools combining diffuse optics and medical ultrasound were explored.

A total of **130 participants** attended both event (75 to the public event and over 45 to the closed panel discussion). For the public webinar, the attending audience came from 13 countries around the globe. While most participants joined from European countries (AT, BE, DE, ES, FR, IT, NL, PL, PT, UK), there were also participants from the US, Taiwan, and the Philippines.

First, consortium partner **Davide Contini**, professor at Politecnico di Milano in Italy, chaired the session, giving an overall view of the agenda and presenting the speakers to the audience.

Then, **Dr. Mitchell Schnall**, the chairman of the department of radiology at the Perelman School of Medicine of University of Pennsylvania and a clinician-researcher, was invited as an external expert. Schnall talked about trans-cutaneous diffuse optics and its importance in medical screening, diagnosis, and post-treatment surveillance. He also highlighted the importance of balancing between the technology push and the clinical need.

Turgut Durduran, ICREA professor and leader of the Medical Optics research group at ICFO, presented the project, summarizing the main goals and objectives. Durduran named the LUCA consortium members introducing the research institutions, the industrial partners, and the end-users clinicians. Their knowledge and expertise have led to the current LUCA device, upgrading the technology readiness level and achieving clinical innovation. The future goal is to standardize and commercialize the device, introducing it to everyday clinical practice.

Finally, **Dr. Mireia Mora**, a physician at the Hospital Clinic of Barcelona and researcher at the August Pi i Sunyer Biomedical Research Institute (IDIBAPS),

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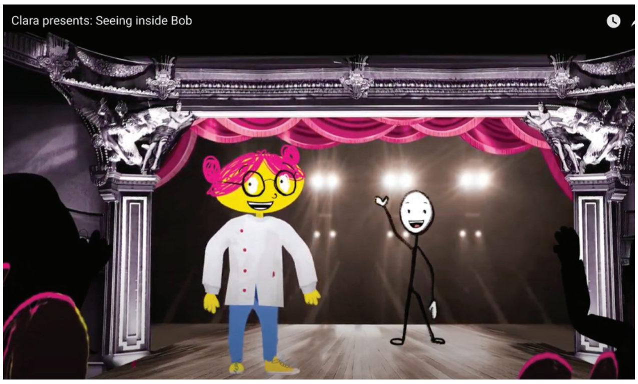
presented LUCA's clinical results. Mora introduced the nodular thyroid pathology, the current tools for diagnosis, and the related clinical problems. She also explained the preliminary results of the two pilot feasibility studies: one conducted in a healthy control group; and the other in a group of individuals with thyroid nodules.

For the closed online panel discussion on November 12, participants joined from five European countries (AT, ES, FR, IT, UK) and the United States.

Panellists of the first session included experts **Mitchell Schnall**, (Chair of Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, USA); **Laura Oleaga** (Chair of Department of Radiology, Hospital Clinic of Barcelona, Spain); **Paola Taroni** (Full professor at Department of Physics, Politecnico di Milano, Italy); **Josep Munuera del Cerro** (Head of Department. Area of Quality, Innovation and Research at the Diagnostic Imaging Department, Hospital Universitari Sant Joan de Déu, Spain), who talked about the different paths for entry of new modalities in diagnostics and screening.

In the second session, experts **Manuel Puig** (Head of Endocrinology and Nutrition Service, Germans Trias i Pujol University Hospital, Spain); **Josep Tabernero** (Head of Medical Oncology Department, Vall d'Hebron University Hospital, Spain & Director of Vall d'Hebron Institute of Oncology (VHIO), Spain); **Jaume Mesquida** (Consultant physician, Critical Care Department, Parc Taulí Hospital Universitari, Spain); **Marco Inzitari** (Director of Intermediate Care & Research, Parc Sanitari Pere Virgil, Spain), talked about the new possible application areas that are still in need of exploration and investigation. ■

CLARA presents...

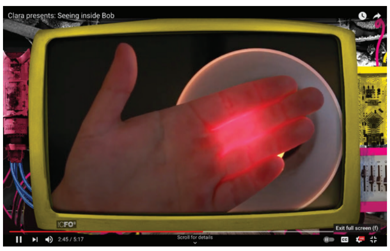


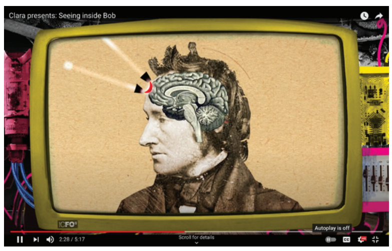
ICFO has launched a new series of videos. In the course of 8 episodes, Clara, a young girl of approximately 12 years old, is interested in understanding and explaining to the general public what diffuse optics is and what applications it may have for the medical world.

The series of videos delves into the world of near-infrared diffuse optics, such as near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS), and tries to explain the devices that are being used for medical care. These biophotonics devices built by the Medical Optics research group at ICFO, led by ICREA Prof. at ICFO Turgut Durduran in collaboration with different networks have been developed to help monitor illnesses such as COVID-19, thyroid cancer, brain injuries for newborns to adults that have suffered an ischemic stroke, among others.

In the first video of the series, Clara explains to Bob, how near infrared red light can be used in a non-invasive way to shine light into the body and understand what is happening inside by watching how the light being absorbed and scattered by the inner tissue.

Stay Tuned for more videos.... watch the video here [LINK]





LIST OF PUBLICATIONS

Learn more about the research carried out within the LUCA project from the consortiums´ scientific publications:

Title	Date	Link
The LUCA device: a multi-modal platform combining diffuse optics and ultrasound imaging for thyroid cancer screening (Biomedical Optics Express)	2021	Link
Recipes for diffuse correlation spectroscopy instrument design using commonly utilized hardware based on targets for signal-to-noise ratio and precision (Biomedical Optics Express)	2021	Link
Neurodevelopmental profile in children with benign external hydrocephalus syndrome. a pilot cohort study. Child's Nervous System	2021	Link
Blood flow response to orthostatic challenge identifies signatures of the failure of static cerebral autoregulation in patients with cerebrovascular disease	2021	Link
Time resolved speckle contrast optical spectroscopy at quasi-null source-detector separation for non-invasive measurement of microvascular blood flow (Biomedical Optics Express)	2021	Link
Monitoring the motor cortex hemodynamic response function in freely moving walking subjects: a time-domain fNIRS pilot study (Neurophotonics)	2021	Link
Non-Invasive Estimation of Intracranial Pressure by Diffuse Optics: A Proof-of-Concept Study (Journal of Neurotrauma)	2020	Link Link
The SiPM revolution in time-domain diffuse optics (Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment)	2020	Link
The SiPM revolution in time-domain diffuse optics (self-archive)	2020	Link
Wearable and wireless time-domain near-infrared spectroscopy system for brain and muscle hemodynamic monitoring (Biomedical Optics Express)	2020	Link
Coherent fluctuations in time-domain diffuse optics (APL Photonics)	2020	Link
In vivo time-domain diffuse correlation spectroscopy above the water absorption peak (Optics Letters)	2020	Link
The Curse of Big Data in Diffuse Optical Spectroscopic Tomography: The LUCA approach (Proceedings of Biophotonics Congress: Biomedical Optics 2020)	2020	Link
A wearable time domain near infrared spectroscopy system (Proceedings of SPIE)	2020	Link
A wearable time domain near infrared spectroscopy system (self-archive)	2020	Link
Instrument response function acquisition in reflectance geometry for time-resolved diffuse optical measurements (Biomedical Optics Express)	2020	Link

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