Currently, to diagnose a peripheral lung cancer, pulmonologists plan the transbronchial biopsy procedure by examining a number of Computed Tomography (CT) scan slices before the procedure. They then manipulate a flexible video bronchoscope into lobe and sub-segmental bronchi as far as the diameter of the bronchoscope permits. Finally, they insert a biopsy forceps through the working channel of the bronchoscope, and blindly perform the biopsy. Consequently, 43%-95% of the procedures fail to reach peripheral targets, depending on size and location. When these failures occur, pulmonologists must repeat the procedure or follow up with more invasive methods that have increased complication rates, such as CT-guided percutaneous needle biopsy with increased level of radiation for surgeon and patient or surgical biopsy with high stress for patient.

We successfully overcame these limitations and enhanced the accuracy and guidance, together with the option of a preliminary optical diagnosis on biopsy site. This main (accomplished) project’s objective was to develop an innovative minimally invasive image-guided system, NAVICAD which uses a novel innovative steerable and electromagnetically tracked biopsy forceps with confocal fluorescence microscopy fiber (pCLE). To achieve this goal, we developed a working prototype of the NAVICAD system including an electromagnetically tracked biopsy instrument with pCLE fiber and we successfully test it in a custom-designed phantoms and large animals.

The project was successfully completed, and for the future, we -the partners of this consortium-plan further development in animal studies, clinical trials and regulatory market approvals. The first clinical trial on human patients for part of the NAVICAD system was approved in Norway for 2018.

Confocal fluorescence microscopy allows physicians to examine potential lung cancers and other diseases on-site before a biopsy and has the magnification that can see individual cell in pulmonary tissue. Therefore it has the potential to prevent more invasive procedures, identify infections and malignant diseases and non-invasively monitor of the treatment for a mass in the airways. The NAVICAD system includes a software module of computer-aided diagnosis (CAD) that assist the bronchoscopist for pCLE image analysis for a fast decision to perform a tissue sampling.

The University of Craiova (UCV), the Project Promoter, and our partners from Norway (SINTEF (P2) and St. Olavs Hospital (P3)) have a track record of collaboration on developing methods to improve cancer diagnosis and treatment via minimally invasive medical devices before the project and will continue the collaboration after this project completion. The specific goals of this project were:

- Development of an innovative instrument for bronchoscopy with electromagnetically tracked and steerable biopsy tip combined with an optical fiber from Cellvizio system.
- Design and implement a CAD system based on ANNs (artificial neural networks) to interpret FDs (fractal dimension) and lacunosity of pCLE images.
- Development of the NAVICAD software for hybrid imaging, navigation and virtual bronchoscopy.

Pulmonologists will be able to use NAVICAD system with navigation and confocal microscopy to image lung tissue from proximal airways down to alveoli in patients presenting pulmonary lesions, to sample and, stage lung cancer as well as monitor the treatment.

Target groups are patients with periferal lung lesions or suspect tissue formations.
Project partnership achieved results

Project Promoter, University of Craiova and Donor State institute, SINTEF contributed actively to the project with available infrastructure relevant to the project, such as an advanced ultrasound and image-guided therapy laboratory at Laboratory of Microtechnology and the Department of Medical Technology. The laboratories are equipped with state of the art ultrasound scanners, various probes, robotics, state-of-the-art computers, tracking systems (optical and electromagnetic based), and a Norwegian National Infrastructure software platform for image-guided therapy, the CustusX platform, in the NorMIT project. The Norway partners have an extensive experience in medical imaging, navigation, software development, and medical instrumentation design and manufacturing, and provided the Romanian partners with important additional expertise and experience necessary for a successful completion of this complex project.

The NAVICAD consortium has a major interest in developing this system, as a concluding result of more than six years of collaboration during the research of hybrid imaging and navigation system from bronchoscopy proven by previous grants and publications. The innovative system we developed as a full working prototype during this project will be further clinically tested and prepared for market by a spinoff developed by our consortium.

In NAVICAD, University of Craiova and Politehnica University of Bucharest together with SINTEF, were focused on developing an open source image guided bronchoscopy navigation system based on iterative specifications from pulmonologists. It is developed from a general open source image-guided intervention software toolkit, the CustusX platform (www.custusx.org) with a simplified graphical user interface (GUI) specialized for planning and guiding bronchoscopy procedures.

SINTEF and Politehnica University of Bucharest have also developed a simplified version of the image guided bronchoscopy system, Fraxinus. The NAVICAD planning module, which does not contain tool tracking. The underlying platform, CustusX, has support for real-time position tracking of tools using either electromagnetic or infrared positioning systems, this functionality will be enabled for the NAVICAD guidance system in conjunction with the new navigation catheter developed by the Romanian team and tested in collaboration in the last phase of the project.

The preclinical testing of the NAVICAD catheter developed by Romanian team was successful tested in a live animal experiment in Trondheim in 2017.

For the guidance part of the NAVICAD platform, Romanian team in collaboration with Norwegian partners refined and tested in the clinic an intraoperative registration method for automatically performing CT-to-patient based registration during the initial phase of the bronchoscopy, i.e. the sedation of the airways. We are using an electromagnetic tracking sensor mounted to the tip of a conventional bronchoscope, and position data is acquired continuously during the sedation phase of a bronchoscopic procedure.

University of Craiova and SINTEF, has set up a laboratory test suite for the bronchoscopy navigation system using the Ultrasonic Bronchoscopy Simulator, LM099, KOKEN CO., LTD, Tokyo, Japan. We have acquired CT images of the phantom, to function as navigation maps similar to the real clinical setting. The phantom is actuated using electrical motors controlled by computer to simulate the respiratory movements of the airways of the phantom to mimic the movements in a human lung. This makes it possible to test and assess the navigation system's accuracy and robustness in a realistic setting.

Based on the diversity of objectives, with interfering clinical and experimental aims, there is a significant added value of working together in a partnership, with clear impact towards both the clinical sector (through the expected development of a novel investigation system for focal lung masses) and also towards the medical industry applications.

Extended collaboration in future Horizon2020 and EEA grant calls between consortium partners
is expected. The future commercialization of the products at national and European level will be pursued by Romanian and Norway partners and will be supported by a spin-off company created at the completion of this project.

St. Olavs hospital/Trondheim University Hospital with the Lung department’s own bronchoscopy rooms are equipped with state-of-the art bronchoscopy equipment, including endobronchial ultrasound bronchoscopes. The department also has bronchoscopes dedicated to research, and both phantom and human testing of navigation technology has been and will be performed in the department’s bronchoscopy rooms. The lung department has access to the navigation system technology to be used in this project (Aurora, NDI).

A core research facility at the hospital is the Future Operating Room, state-of-the-art operating rooms, a collaboration between the hospital, SINTEF and the university NTNU. 50% of the time is dedicated to research, including human, animal and basic research. They are equipped with state-of-the art intraoperative radiology equipment. The NAVICAD system proposed in this project can help pulmonologists accurately obtain tissue samples from peripheral lung nodules and, thereby, improve the rate of successful biopsies. This interdisciplinary collaboration with consortium engineers and physicists are important for Partner’s medical doctors and complement his previous collaboration on projects.

The work assignments for partners were agreed in such a way that no duplication of work will take place. The Consortium's interdisciplinary is evident from the description made above; physicians will work together with biomedical engineers, programmers and international recognized medical experts for the success of the project and for putting on the market an advanced product.

St. Olav’s Hospital has contributed to all phases of the project together with both the technological team at SINTEF and the University of Craiova and Politehnica University of Bucharest. In the clinic we have been able to test equipment in realistic setting, assess the accuracy and feasibility and also study the visualization solutions during real patient procedures when the NAVICAD planning and guidance system is used alongside the conventional systems used for bronchoscopy and sampling of peripheral lesions. The clinical goal is to increase the success rates of biopsies using better planning and guidance system developed by the Norway-Romania team collaboration.

Industrial inspiration and involvement in the consortium’s effort is necessary as the project claims industrial applicability of the result. Extended collaboration in future Horizon2020 calls between consortium partners are expected.

**Socio-economic impact**

The present project aligns with the objectives of this consortium, which combines research and development of novel medical devices with clinical applications.

The research project in itself uses some of the imaging methodology, which currently is under development in other projects as guidance using electromagnetical tracking, registration and image fusion with CT scans.

The proposed innovative system for transbronchial biopsy using image and electromagnetic guidance with augmented diagnostic provided by CLE system, and all technologies developed can only be devised by a multi-disciplinary team consisting of dedicated biomedical engineers, medical doctors, and programmers working together. Based on the diversity of objectives, with interfering clinical and experimental aims, there is a certain added value of working together in the partnership, with clear impact towards both the clinical sector (through the expected development of a novel investigation system for focal lung masses) and also towards the medical industry applications.

According to statistics for 2010, worldwide, lung cancer is the most common cause of cancer-related death in men and women, and is responsible for 1.3 million deaths annually. Surviving lung cancer
is closely linked to the cancer’s stage. Unfortunately, patients often present only after their symptoms are at an advanced stage. Therefore it is essential to diagnose the small lesions early. For these small lesions, it is important to obtain tissue samples in sufficient quantities to establish the diagnosis. NAVICAD system can help pulmonologists accurately obtain tissue samples from peripheral lung nodules and, thereby, improve the rate of successful biopsies. Currently, small peripheral lung nodules are difficult to biopsy under the conventional bronchoscopic technique, since they are often too small to see under fluoroscopy. Moreover, biopsy forceps cannot be accurately guided through smaller bronchi beyond the view of a traditional bronchoscope. The proposed system will allow biopsy forceps to be guided through the smaller bronchi to biopsy small peripheral nodules, beyond the point that a flexible bronchoscope can reach.

Moreover, with a virtual assistance system synchronized to an actual video bronchoscopy, and with integration of Cellvizio CLE fiber integrated in our biopsy instrument, pulmonologists will “see behind the mucosa” of the airway in real-time. Our CAD module gives to the bronchoscopist a powerful feature for a fast automatic interpretation of Cellvizio images during the procedure. We anticipate that the accuracy of transbronchial biopsy will significantly increase as a result of the non-invasive navigation technology we are proposing. Additionally, this noninvasive technology is expected to lower the complication rate of biopsies, including the rate of pneumothorax. We anticipate that the risk of pneumothorax for our system should be less than 1 percent, compared with the risk of 23 to 38 percent for CT-guided transthoracic biopsy.

Conclusions

This project brought together experts in visualization, image registration and segmentation, biomedical engineering, microscopy and clinicians to create a minimally invasive, image-guided system that will provide more accurate biopsy sampling, especially for targets located in the periphery of the lung.

The image-guided system developed allows biopsy forceps to be guided through the smaller bronchi to biopsy small peripheral nodules, beyond the point that a flexible fiber-optic bronchoscope can reach. Moreover, with a virtual assistance system synchronized to an actual video bronchoscopy and microscopy, NAICAD system will enable pulmonologists to “see behind the mucosa” of the airway in real-time. Lung nodules can be distinguished with different colors in virtual bronchoscopy and microscopy, allowing the pulmonologist to more accurately guide biopsies.

The accuracy of transbronchial biopsy significantly increases as resulted from testing, due to the noninvasive technology we developed. Additionally, this noninvasive technology is expected to lower the complication rate of biopsies, including the rate of pneumothorax. We anticipate that the risk of pneumothorax for our system should be less than 1 percent, compared with the risk of 23 to 38 percent for CT-guided transthoracic biopsy. Furthermore, the image guidance provided by our system will help new practitioners master the procedure faster.