Newsletter

Spring 2021

ProCAncer-I

In this issue

European Commission

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Editorial

Editorial by Prof Manolis Tsiknakis, Coordinator of ProCAncer-I project

The ProCAncer-I consortium welcomes you to our first newsletter!

We are very happy that our project ProCAncer-I on dealing with prostate cancer was funded by the EU and that through its successful implementation, we may contribute to the better diagnosis, management and therapy of prostate cancer.

In Europe, prostate cancer (PCa) is the second most frequent type of cancer in men and the third most lethal. Considering that about 1,300,000 citizens of the European Union are estimated to have had a prostate cancer diagnosis in the last five years, the severe socioeconomic burden for health services and the negative effects on the quality of life of patients call for immediate actions.

The fact is that in the domain of PCa detection, treatment and/or management, several pressing and unmet needs do currently exist. Current screening practices based on prostate serum antigen (PSA) blood test and digital rectal examination (DRE) have led to significant overdiagnosis, i.e. the diagnosis of indolent tumours which, once diagnosed, are treated as a deadly disease with radical therapies that severely affect patient quality of life.

At the same time, Artificial Intelligence (AI) is transforming the field of healthcare in general and medical imaging in specific. Worldwide interest in artificial intelligence (AI) applications, including imaging, is high and growing rapidly, fueled by the availability of large datasets ("big data"), substantial advances in computing power, and new algorithms. Recent advances in AI methodologies have made great strides in automatically quantifying radiographic patterns in medical imaging data. Deep learning, a subset of AI, is an especially promising method that automatically learns feature representations from sample images and has been shown to match and even surpass human performance in task-specific applications.

The project "**ProCAncer-I: An AI Platform integrating imaging data and models, supporting precision care through prostate cancer's continuum**", focuses on developing advanced AI-base models that go beyond current SoA by deciphering non-intuitive, high-level medical image patterns in a) discriminating indolent from aggressive disease, b) early predicting recurrence and detecting metastases or c) predicting the effectiveness of therapies. To achieve this, the project will generate a large interoperable repository of health images, and a scalable high-performance computing platform hosting the largest collection of PCa Magnetic Resonance Images (an estimated 1,5 Million images coupled with accompanying clinical data) to be used for developing these robust PCa AI models.

ProCAncer-I recognizes that while computational techniques to build AI-based models for medical care have been pursued for years, there is currently a more urgent need to build AI solutions that can be trusted in order to be accepted by regulating bodies and adopted by the clinical community. Although AI-based models hold promise for improving care, especially in imaging diagnosis, robust evaluation of AI-based software before implementation is needed to reduce patient and health system risk, establish trust, and facilitate wide adoption. Towards this direction, the project is devoting significant efforts in developing the methodological framework and tools to support the fairness, robustness, traceability and explainability of the models to be developed.

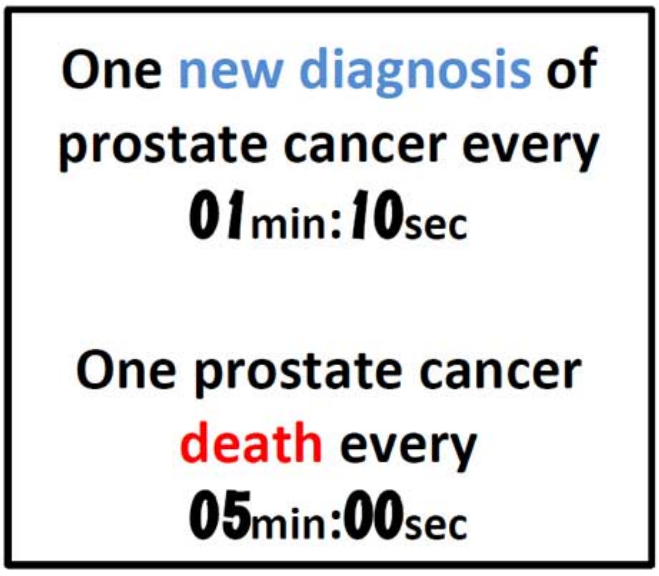
The ProCAncer-I project (https://www.procancer-i.eu/) brings together the best of bread in the technological, scientific and clinical domains, a unique team of 20 institutions from 12 different countries from Europe and elsewhere. It combines expertise from academia and the market with vibrant and dynamic SMEs with a proven track record, as well as non-profit research institutions and leading university hospitals in the field of prostate cancer. It's a balanced consortium geographical wise with partners from East and West Europe as well as from Turkey and the US.

MRI based Artificial Intelligence tools will improve the management of patients with prostate cancer

By Prof. Daniele Regge [Chief of the Radiology Unit, Candiolo Cancer Institute, Torino-Italy] and Simone Mazzetti [Candiolo Cancer Institute, Torino-Italy]

Prostate cancer is the most frequently diagnosed tumour in Europe with one new cancer detected every 70 seconds and one related death every five minutes. Prostate cancer has often a devastating impact on patients quality of life, due to the necessity to undergo unpleasant and debilitating treatments.

When these tests fail to identify prostate cancer, the patient's long-term health and well-being might suffer an irreversible impact, because the later the diagnosis, the more likely that cancer will have grown and spread to remote parts of the body becoming a deadly disease. Hence, the main clinical challenges for the future will be to identify prostate cancer with high accuracy, as early as possible, to stratify patients according to disease aggressiveness and to tailor therapy (or non-therapy) based on the risk of progression, comorbidities and life

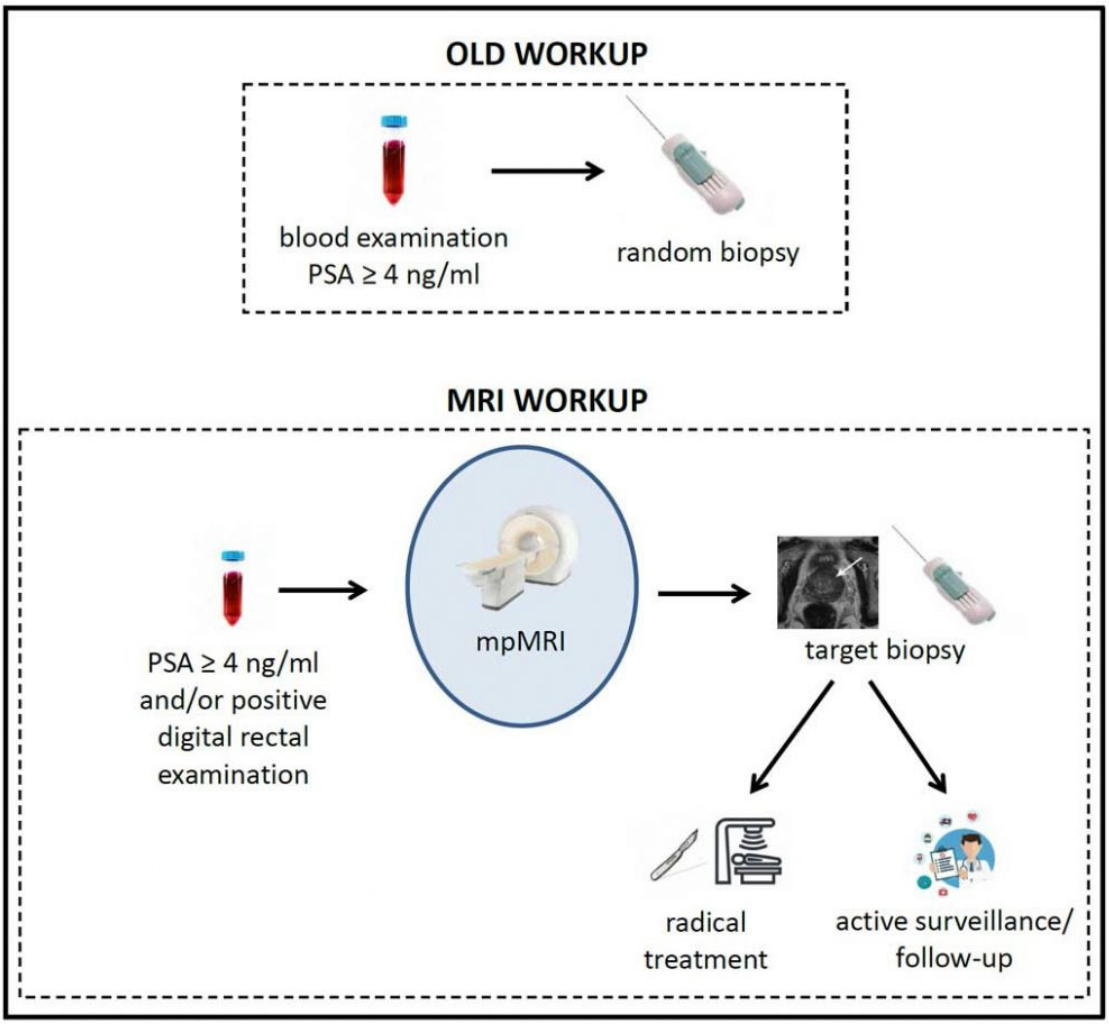


The prostate cancer clock

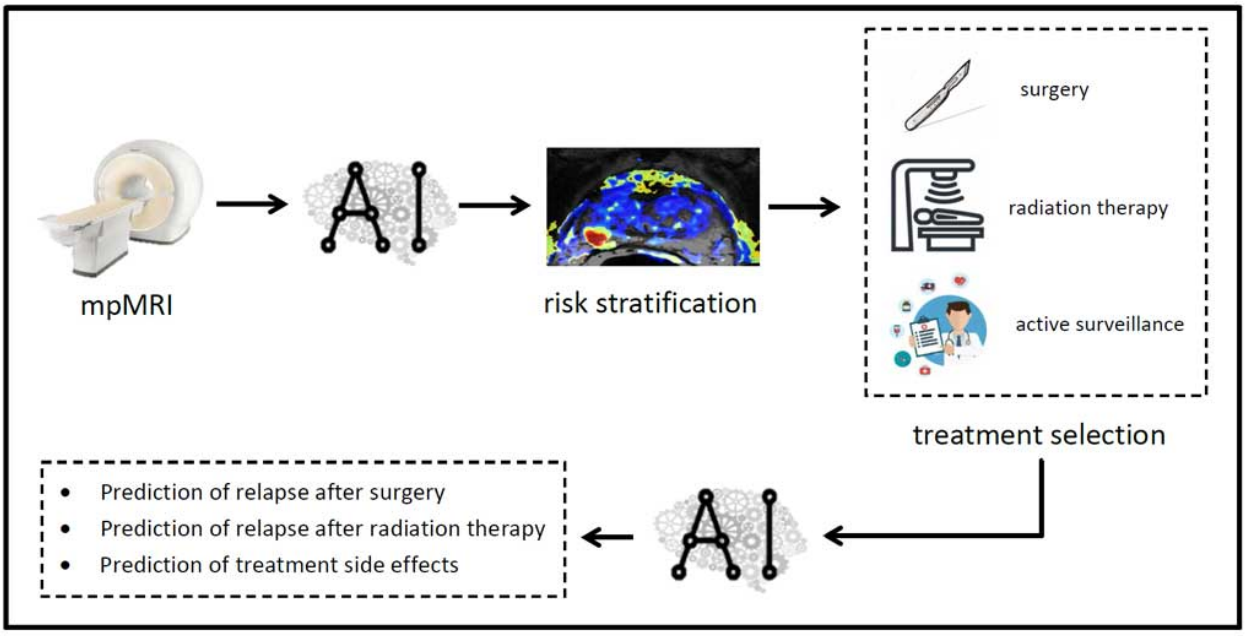
expectancy. Even when prostate cancer is correctly detected, decisions must be taken on whether to treat or simply to monitor patients considering that treatment-related complications cannot be neglected, with as many as one in five men developing long-term urinary incontinence, and up to two in three erectile dysfunction.

Since 2020, the European Urological guidelines strongly recommend multiparametric magnetic resonance imaging (MRI) in men with suspicion of prostate cancer. MRI is a non-invasive technique providing a large amount of information for the management of prostate cancer patients. It has a high sensitivity in identifying men with clinically significant tumours, which will require whole gland treatments such as prostatectomy or surgery. Moreover, when the examination does not detect cancer there will be a high probability that clinically significant cancer is not present, avoiding these patients unnecessary biopsy. Finally, MRI can improve the performances of biopsy by guiding the needle directly to the tumour. Risk stratification of patients with MRI, allowing tailored treatment, will represent another piece to the puzzle towards the reduction of overtreatment and improvement of patients quality of life.

However, MRI is a time-consuming examination, it requires reporting by experienced radiologists and dedicated facilities. For this reason, the use of MRI for prostate diagnosis is still not widespread within the EU borders. The EU project ProCAncer-I seeks to deal with some of the current limitations of MRI by developing advanced artificial intelligence (AI) based processing tools aimed at improving the detection and characterization of prostate cancer lesions, with the ultimate aim of bringing medicine from the era of "sick care" to that of "prevention". Indeed, AI has the potential to value information hidden in medical images and obscure to human perception, enhancing cancer detectability, identifying individual characteristics of disease aggressiveness, predicting treatment response and side effects, and finally understanding better disease prognosis.



Comparison of prostate cancer diagnosis without and with magnetic resonance imaging



Clinical applications of the ProCAncer-I project

The major challenge of a common anonymization strategy

By Prof Kostas Marias [Foundation for Research and Technology – Hellas (FORTH)], Ioannis Karatzanis [Foundation for Research and Technology – Hellas (FORTH)] and Katerina Nikiforaki [Foundation for Research and Technology – Hellas (FORTH)]

Anonymization is an irreversible processing operation that consists of using a set of techniques in such a way as to make it impossible, in practice, to identify the person by any means. This process is challenging when dealing with DICOM formatted data. The complexity lies in anonymizing while preserving the value of the DICOM dataset. As a result, the process of defining the optimal data anonymization strategy, especially for data sharing purposes, has proven to be a major technical challenge.

From the beginning of the ProCAncer-I project, it became obvious that different clinical sites had a variable degree of experience and deployed a number of different technological solutions to anonymize data. In the data sharing context, if there is no common strategy regarding anonymisation, it can create discrepancies and heterogeneity in the data collected. Having in mind that one of the goals of the project is the creation of the ProstateNET, a publicly accessible mpMRI data repository, it was of utmost importance to deal with this from the beginning.

For these reasons, a common anonymization strategy had to be defined and adopted, taking into consideration all different data types to be collected. A series of discussions took place between legal, clinical and technical partners in search of common ground. At the same time, an exhaustive analysis of relevant available technological solutions took place in order to explore the functionalities of each tool and evaluate its performance on the specific type of data the project is dealing with. At the end of the process, the partners agreed to adopt a 'whitelisting' anonymisation strategy. The whitelisting approach was considered appropriate for both retrospective as well as prospective data. The major decisions reached regarding the anonymization process are described below:

1. Each Clinical institution will use the tools that are currently used for data anonymization within the hospital site. Such tools are usually classified as 'blacklisting tools', meaning that a dedicated software removes or modifies selected tags from the series' list of DICOM tags. These tags are usually tags with personal information or tags with information that can lead to the identification of an individual. All other DICOM tags are maintained when using the black-listing anonymization approach. It is obvious that this process may generate heterogeneities.
2. In order to produce a homogenous dataset in terms of the metadata used for the DICOM headers, ProCAncer-I will apply a second anonymisation layer within each hospital. During this phase, only the absolutely necessary DICOM header information required for deciphering

quantitative information and AI modelling will be preserved discarding all the other DICOM tags. This approach, referred to as 'whitelisting' will retain only those non-personal health information required for AI modelling and at the same time, it will homogenise the anonymized data before final upload. The 'whitelist' anonymization process will be performed through the established RSNA DICOM Anonymizer tool that was customized using a custom configuration script. This configuration script implements the DICOM whitelist that the project defined following an iterative process that has been coordinated by Ioannis Karatzanis and Katerina Nikiforaki from FORTH.

3. Once the DICOM data goes through the whitelist anonymization, it will be uploaded to the ProCAncer-I repository as 'anonymised data'.

A very important decision taken is the fact that all data will be anonymized within the security domains of clinical institutions before data uploading to the ProCAncer-I repository. In parallel, the experienced team of Prof. N. Forgo (UNIVERSITAT WIEN) who provide legal guidance to the project, together with legal teams and DPOs of all relevant partners will continuously monitor the risk of data re-identification throughout the project, in order to eliminate any such re-identification risk. Concurrently, the technical partners of the project will provide continuous support to the clinical institutions for the efficient implementation of this very important task in line with the common strategy agreed upon. They will also work in close collaboration with clinical partners to ensure that this process is optimally implemented in the context of a busy clinical environment. Overall, the aim for an easy to implement workflow has been successfully established, performing robust anonymization in a homogeneous manner across all partners. At the same time, a common approach in anonymization and homogenization of the process is also being discussed across all the 'AI for Health Imaging' funded projects.

Interview with Dr. Nickolas Papanickolaou on the vision of the project

By Nickolas Papanikolaou, Scientific Coordinator of the project [Principal Investigator in Oncologic Imaging at the Fundação Champalimaud]

Why did you select prostate cancer as the center of your research? What kind of clinical unmet needs will be addressed in ProCancer-I?

Prostate cancer is among the most prevalent cancers with rising trends, affecting a significant number of patients after the age of 50. Hopefully the vast majority of cases are indolent and only few of them are aggressive that need immediate treatment. With the advent of improved detection methods based on serum PSA, overdiagnosis and overtreatment was the result, leading to the need not only to detect but also to characterize prostate cancer cases according to their biological aggressiveness, and possibly spare invasive and toxic treatment in those patients that they would not benefit due to low aggressive tumors.

How does ProCancer-I differentiate from other EU funded projects? What innovations will it bring to the clinical setting?

ProCancer-I is unique not only due to the comprehensive assessment of unmet clinical needs spanning throughout the whole disease continuum, but also due to the availability of data dealing with the quantity, quality and diversity demands, necessary for proper training and validation of AI models. ProstateNET, the platform to be built collecting available data, is targeting the unparallel number of 1.5 million prostate images, while its existence and maintenance will give unique opportunities to tackle important unsolved problems and create value for our patients, physicians as well as the health care systems.

In ProCancer-I you are using AI approaches to analyze the data. What would be the role of AI – acting autonomous or as a virtual assistant of the end users?

Europe already decided to support and develop human centric AI. That is a decision that we need to serve and adapt our approaches to meet the necessary objectives. The prostate AI models that will be developed from the ProCancer-I consortium will provide valuable data and informed insights to the end-users helping them to decide among different treatment options, weight the benefits and consequences of specific therapeutic schemes. It is our intention and obligation to facilitate the latter by increasing the trustworthiness of the developed models by providing evidence on the model decision mechanisms, abandoning "arrogant" AI approaches

presented so far, where AI models have always an opinion no matter how wrong or how right that can be. Concepts like FAIRness, identification of bias, interpretable algorithms are in the DNA of our methodological approaches.

Why is the collection of data and analysis of data a core activity of the ProCAncer-I project?

The size and the diversity of the data will create immense opportunities towards answering important methodological dilemmas that are challenging and relate to whether someone should harmonize and standardize the data working in "laboratory" conditions, or would choose a more "dirty" approach to expose the models in real world data and therefore make them more robust and reproducible. Hybrid approaches using deep and handcrafted features, centralized and federated learning schemes, training from scratch or transfer learning methods in a scale that hasn't been tried out before will constitute our methodological approaches, expecting that will bring us steps ahead of the current state of the art.

Legal and Ethical Aspects of ProCAncer-I: The Anonymisation of Personal Data

By the legal team of ProCAncer-I, The University of Vienna Department of Innovation and Digitalisation in Law (UNIVIE)

Given the innovative nature of the technology being developed in the ProCAncer-I project, complex legal questions have arisen concerning the processing of personal data. The technical process of anonymisation can be a complex one, particularly when considering whether medical images can lead to the re-identification of a data subject. The University of Vienna Department of Innovation and Digitalisation in Law, known as UNIVIE on the ProCAncer-I project, leads WP2 on the legal and ethical aspects of the project. Therefore, UNIVIE is working closely with all partners to assist in ensuring that all personal data is anonymised before being processed in the project, thereby minimising or altogether eliminating risks to the rights and freedoms of the data subject.

The project aims to process data related to prostate imaging. Within the EU data protection regime, the EU General Data Protection Regulation (GDPR) regulates the processing of personal data. Personal data is defined according to Article 4(1) GDPR as "any information relating to an identified or identifiable natural person", known as the data subject. However, not all personal data is created equally. The GDPR distinguishes between standard personal data such as one's name, phone number or photograph, and special categories of personal data. Special categories are those which are more sensitive and due to their nature may pose higher risks to the rights and freedoms of the data subjects when processed. As defined in Article 9(1) GDPR, data concerning health is considered to be one of these special categories. Given that medical images showing prostate cancer (PCa) with the attached patient data constitute data concerning health, any such processing is forbidden unless it is permitted in line with one of the exceptions in Article 9(2) GDPR. However, the aim of the ProCAncer-I project is to anonymise all personal data related to PCa before bringing the data to the project to assist in the development of the project. According to Recital 26 of the GDPR, the GDPR does not apply to anonymous data, that is, data that does not relate to an identified or identifiable natural person. However, the task of determining whether data relates to an identified or identifiable natural person is not a simple one. The GDPR asks data controllers to consider the means reasonably likely to be used to re-identify the data subject either by the controller or another person whether directly or indirectly. Consideration should be given to "objective factors, such as the costs of and the amount of time required for identification, taking into consideration the available technology at the time of the processing and technological developments" (GDPR, Recital 26).

Guidance from the Article 29 Data Protection Working Party (Opinion 05/2014 on Anonymisation Techniques, page 7) says that "anonymisation is a technique applied to personal data in order to achieve irreversible de-identification", in such a case there is an assumption that the personal data originally collected must have been done so in compliance with data protection law. As such, the partners in the ProCAncer-I project must ensure not only the suitability of the anonymisation techniques, but they must also ensure that the personal data being anonymised was collected in accordance with the GDPR and EU ethics standards. Furthermore, the act of anonymisation itself must be compliant with data protection law because until the personal data is anonymised, it remains subject to the GDPR.

Presentation of partner Radboud UMC

Major Clinical partner of the project | By the Radboud UMC

Radboudumc is one of the leading centres for prostate cancer imaging worldwide. Within the ProCAncer-I project, two groups of the Department of Imaging of Radboudumc are represented. The Diagnostic Image Analysis Group (DIAG), under the Departments of Radiology, Nuclear Medicine and Anatomy, has pioneered the development of prostate computer-aided diagnosis (CAD) and decision support systems, with a scientific archive of nearly 10.000 anonymized mpMRI scans.

In recent years, artificial intelligence (AI) has become indispensable for medical image analysis. Deep learning (DL) is able to capture a complex hierarchy of features; reaching competitive performance relative to expert radiologists. The goal of DIAG in this context is to develop automated DL-CAD algorithms that can identify potential biomarkers in prostate MRI and reliably discriminate clinically significant lesions from indolent cancer and benign tissue. In turn, DIAG aims to improve diagnostic certainty throughout the clinical workflow of prostate cancer management and facilitate stronger patient outcomes.

The Minimally Invasive Image-Guided Intervention Center (MAGIC) is also part of the Department of Radiology and Nuclear Medicine. MAGIC has its roots in MRI-guided prostate treatment and has expanded its expertise to image-guided oncologic interventions such as biopsy of prostate, bone and liver and (non-) thermal ablations of pancreas, liver, kidney, prostate and vascular malformations. The group currently consists of various physicians and technical physicians, combining both technical as clinical expertise to create a significant impact on healthcare and bring our technologies to daily clinical practice.

A large research theme within the MAGIC group is related to interventions and innovations regarding prostate cancer. As the field of AI for prostate cancer is rapidly advancing, the clinical implementation of these techniques is lacking. During the ProCAncer-I project, researchers from MAGIC will focus on bridging the gap between advanced AI innovations and the clinical implementation and feasibility of these techniques. With this, MAGIC aims to facilitate a significant clinical impact of AI in the clinical workflow and management of prostate cancer.

Presentation of partner UNIVIE

Legal partner of the project | By the University of Vienna – Department of Innovation and Digitalisation in Law (UNIVIE)

The University of Vienna is the oldest University in the German-speaking world, and the Department of Innovation and Digitalisation in Law is the newest addition to the University's Law School. Having been founded in 2017, the Department is dedicated to legal research on all issues related to information and communication technologies and more broadly technology and the law. Research areas include EU data protection law, privacy law, intellectual property law and the law related to information technologies as well as e-evidence, e-commerce and consumer protection law.

In addition to teaching obligations and work with leading industry stakeholders, much of the work at the Department focuses on third-party funded research projects under the umbrella of the EU Horizon 2020 framework program for research and innovation. Working on several projects related to the development of innovative technologies in medicine and healthcare, aimed at assisting clinicians

and researchers in the identification, treatment and further research of a number of health conditions, UNIVIE acts as the legal and ethical partner on these projects. This interdisciplinary work not only assists clinicians and technical organisations in understanding and complying with the applicable law, but it contributes to the academic and practical legal area. Given the relatively new nature of the law in this area and the even more novel nature of the technologies, UNIVIE is often faced with complex legal questions. Such questions can stem from the type of data being processed, the means of processing employed, the various international partners involved in the projects and the potential future implications of the technologies being developed.

On the ProCAncer-I project, UNIVIE is responsible for leading WP2 concerning the legal, ethical and societal considerations of the project, thereby serving as the single point of contact for all internal and external stakeholders on legal and ethical questions. In particular, UNIVIE validates the processing of personal data collected before the commencement of the project, personal data collected during the project, the conditions for the anonymisation of the personal data and data sharing and IP considerations.



From left to right: Prof. Dr. Nikolaus Frogó / Max Königseder, LL.M. LL.M. / Emily Johnson, LL.M. LL.B:

news

ProCAncer-I in the Health IT Conference

Dr. **Nickolas Papanikolaou**, participated in the **Health IT Conference**, that was held online (15&16 June 2021). The main objective of the conference was "**Health Informatics in the Covid-19 period**", a strategic dialogue for the real upgrade of Information in Health.

Dr. Papanikolaou presented **ProCancer-I** project in the section *Greece's presence in European digital innovation actions*.

The aim of the Conference was the digital transformation of the country. An emphasis was given on issues such as pandemic management through digital tools and applications, e-government in the National Health System and interoperability between public and private health service providers. Citizens' mobile health services, telemedicine, big health data, artificial intelligence in health etc., were also discussed in the e-Health Strategy.

Fighting prostate cancer with over 1.5 million MRI images

Men die about five years earlier than women across the world. As initiatives to boost awareness of men's health unfolded in November, an international project is bringing the forefront of AI research to tackle prostate cancer (PC), the second most frequent type of cancer in men and the third most lethal in Europe.

Over the next four years, the ProCAncer-I consortium will receive €10M EU funding to develop advanced AI models to meet clinical needs in diagnosis, metastases detection and prediction of response to treatment, by creating the world's largest PC MRI database and validating solid algorithms.

ProstateNet: over 1.5M images to display prostate cancer

15 institutions across the EU, Turkey and the UK will work to gather over 1.5 million prostate cancer images taken in 17,000 multi-parametric MRI examinations into a unique collection called ProstateNet. Building a strong dataset is a must to unleash the power of deep learning in clinical practice, according to Nickolas Papanikolaou, Principal Investigator in Oncologic Imaging at Antonio Champalimaud Foundation, in Lisbon, and Scientific Director of the consortium. 'The highest dataset that is publicly available, so far, comprises a few hundreds of examinations. But, to provide meaningful outcomes, you need to provide thousands. The reason deep learning fails to provide clinical value now is that you need big datasets,' he pointed out.

The project will count with the participation of renowned radiologists such as Daniele Regge, from the University of Torino, who serves as Clinical Director, and Emmanuele Neri from the University of Pisa, to name some. The consortium will also develop and maintain a centralised data repository, which

Dr. Nickolas Papanikolaou
Source: Champalimaud Foundation

will become available for third parties through controlled access. A special governance committee will be formed to examine applications and grant or refuse access.

The third goal is to develop AI models that can harness information contained in these huge amounts of data, to answer clinical unmet needs along eight defined clinical use cases tackling the whole disease continuum - from detection all the way to treatment-related prediction or toxicity. This holistic approach was probably the reason the project received EU support, according to Papanikolaou: 'We believe we have exhausted all the important pitfalls and current limitations in clinical practice, and we will try to solve these pitfalls through technology use.'

Read more: https://healthcare-in-europe.com/en/news/fighting-prostate-cancer-with-over-1-5-million-mri-images.html

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