## Project plan and description:

# Improved cancer diagnostics using artificial intelligence

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## Scientific title

**En:** Artificial intelligence for automated PET/CT image analysis of cancers in a data warehouse framework.
**Da:** Kunstig intelligens til automatiseret PET/CT-analyse af kræft i en data warehouse opsætning

## Content

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## Brief Project Description

In modern cancer treatment, disease assessment is typically carried out by involvement of several medical specialties. Each specialty is concerned with obtaining the most accurate diagnose using biomarkers specific to their field. Accordingly, each create predictive models based on local data, even though measurements performed in different specialties could interact in ways which are currently overseen. In addition, the amount of information about each patient is more than what can be evaluated by one person. These factors lead to a risk that results with crucial impact on patient treatment are overseen in the diagnostic process, increasing the risk of late diagnose and suboptimal treatment.

Combined positron emission tomography and x-ray computed tomography (PET/CT) is a central cancer assessment tool. However, PET/CT-based biomarkers cannot currently be collected routinely, as this requires comprehensive and expensive manual workflows. Hence the purpose of our project is to use artificial intelligence to automate the collection of PET/CT biomarkers and combined these with other clinical information such as biochemistry, microbiology, pathology and genetics in a learning system, which can improve prognostic models over time and be used as a clinical decision support system to optimize patient treatment.

We will approach this task by optimizing, validating and implementing artificial intelligence models to carry out automated PET/CT analyses and collection of biomarkers. We will then combine PET/CT-biomarkers with other diagnostic information in a data-warehouse. Using data-ware house information across specialties, we will improve current prognostic models to predict the risk of side-effects, recurrence and mortality. This will first be done for head and neck cancer patients and be followed by an extension of the methods to other patient groups.

Our prognostic models will enable a systematic development of treatment protocols, which can lead to earlier and better diagnostics and treatment. Before our prognostic models can be used in treatment protocols, these must be tested in randomized clinical trials, which is an integral part of the project, where the project group will ensure, that our results will create direct value for Danish cancer patients. Out methods for automated workflows and collection of biomarkers can be implemented within the timeframe of this project and will at the same time enable analyses, which today are only available for few selected patients, for a considerably larger group of patients.

# Project Description

## Background

### PET/CT-biomarkers hold a vast potential in cancer diagnostics

PET/CT imaging enables physicians to simultaneously evaluate functional and anatomical diagnostic information. This quality has made the technique an essential state-of-the-art tool in oncology, where it is used regularly to support key decisions about patient treatment [1]. A promising new use of PET/CT is the collection of quantitative biomarkers based on the images (PET/CT-biomarkers) for the development of more accurate prognoses.

The expectation is, that PET/CT biomarkers can lead to an improved stratification of patients for the various treatment protocols. In this regard, it has been shown, that PET/CT-biomarkers such as radioactive glucose uptake (18F-FDG) in the tumor as well as some organs at risk, can be used to predict the probability of side-effects, recurrence and mortality in HNC, lung cancer and lymphoma. Other promising PET/CT-biomarkers include maximal standardized maximal standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), peak standardized uptake value corrected for lean body mass (SULpeak) [2]–[10]. In addition, new results indicate, that cellular PET-activity in healthy tissues, such as the intestines, could be a promising biomarker with considerable value [11], [12].

Before PET/CT biomarkers can be used routinely, however, it is necessary to create more standardized methods for collecting biomarkers, which can ensure increased levels of reproducibility and stability between health care professionals, institutions, equipment and over time [13], [14]. Further, extraction of biomarker information from the scans are currently done manually and are very time consuming, resulting in under-powered studies and hampering clinical implementation.

### Combination of diagnostic biomarkers across specialties leads to improved prognostic models

Considering the current organization of the diagnostic system, cancer patients are usually investigated by the involvement of several medical specialties, including nuclear medicine, radiology, pathology, microbiology, immunology, biochemistry and genetics. Research in each of these specialties is characterized by an increase in the level of specialization over time. While this can be positive for one specialty, it also leads to a vast increase in biomarkers, causing an exponential growth in the number of possible interactions across specialties that are never considered. Hence, across specialties, we have more information, than what can be evaluated by physicians without the aid of advanced decision support systems. In effect, a systematic risk exists in the current health care system, that we do not consider the prognostic factors and interactions, that lead to optimal diagnosis and treatment.

### Artificial intelligence is the solution for creating prognostic models across specialties

Artificial intelligence (AI) is a collective term for information-technological methods, that are characterized by the ability to automatically adapt to new situations. Recently developed AI-methods have the ability to analyze and test an overwhelmingly large number of factors and their interactions systematically; for instance, to achieve the best possible prognostic models. AI-models in a health care context can be automatically improved by re-optimizing models every time a new treatment result or biomarker is registered. Because of this, AI can be used to create an automatically learning health care system, which improves its prognostic accuracy for various diseases over time by identifying the optimal inclusion and combination of prognostic factors. These prognostic models can later be used for as quantitative decision support systems guiding the choice of treatment protocols and randomized clinical trials each patient could take part in [15].

In the field of PET/CT, AI has been used for MRI-based attenuation correction, automated tumor detection, prediction of lymph node metastases, image registration, image synthesis and to increase reconstruction quality [16]–[31]. However, research about the use of for PET is lagging when it comes to its most important use: The possibility to automate workflows and collect biomarkers to enable better prognostics and hence an improved treatment result for our patients [32].

## Establishing a data warehouse as a prerequisite for artificial intelligence across specialties and collaboration with leading players

Before the vast potential of AI-models in clinical diagnostics can be fulfilled, it is necessary to collect diagnostic information from multiple specialties in a diagnostic storage system known as a *data warehouse.* For this purpose, Copenhagen University Hospital (Rigshospitalet) is a leading institution with the establishment of the Centre of Excellence for Personalized Medicine of Infectious Complications in Immune Deficiency (PERSIMUNE) data warehouse and Datacenter Øst, which collects clinical and paraclinical information form a large number of patients. However, both data warehouses lack the integration of diagnostic imaging biomarkers. Hence, we will establish such an integration by optimizing, validating and implementing automatic AI-based image analysis, tumor delineation and extraction of biomarkers from PET/CT scans of cancer patients, and return this information for correlation with relevant data available in the PERSIMUNE data warehouse. During this development and validation process, we will work with the School of Biomedical Engineering and Imaging Sciences at Kings College in London, which is an internationally leading institution in the field of AI for medical imaging (the applicant has dual affiliation with Rigshospitalet and Kings College London). Finally, we will use PET/CT-biomarkers together with other diagnostic information to develop improved prognostic models.

## AI-based prognostic models for head and neck cancer (HNC) and other cancers

According to the World Health Organization, HNC leads to more than 300.000 deaths each year globally. In Denmark, the number of cases is 9 per 100.000 citizens, which is much above the global average of 5 cases per 100.000 citizens. In addition, the number of HNC patients in Denmark is increasing also in younger people due to the increased spread of human papilloma virus (HPV).[33]

Meanwhile, PET/CT has shown considerable value in HNC, where the technique is used routinely for staging, treatment planning and response evaluation.[34], [35] Among others, it has been shown, that PET/CT increases the probability of detection of malignant lymph nodes, metastases and unknown primary tumors. [36]–[38] Because of this, we choose to initiate this work by focusing on showing the value of AI in a data warehouse setup for this group. However, as our final goal for this work, we wish to implement the developed infrastructure and the possibilities it enables to increase prognostic accuracy for other cancer patient where PET/CT is used.

## Purpose

The lack of information sharing across medical specialties leads to a risk of delayed diagnosis and suboptimal treatment. Hence, the current design of information systems and health care organization has an imbedded risk of hurting patients.

Our purpose is to diminish this risk using the latest developments in computer science to fulfill the potential of the vast amount of health data already registered for each patient. With this approach, we wish to draw on the benefits of the digitalized health care system to improve diagnostics and treatment of patients with cancer. Cancer patients are especially exposed to large numbers of diagnostic tests and complex treatments, and in this project, we will focus on enabling automated collection of biomarkers from PET/CT images and merging these with clinical, pathological and biochemical data, enabling the development of improved prognostic models based on a large amount of patient data.

We will use scans and data from patients with head and neck cancer (HNC) for proof of concept. However, the developed methods for automated collection of imaging biomarkers and merging with data from other specialties are generic and will be accessible for optimization to other cancers and medical specialties. Thus, this project is the first step towards, the vision of enabling data sharing across all specialties for all cancer patients, and reducing the rates of recurrence, side-effects and mortality.

## Hypotheses

It is our main hypothesis, that AI can be used in combination with data warehouse solutions to improve prognostic models, leading to an improved patient treatment with decreased rates of recurrence, side-effects and mortality. This will be confirmed/rejected by investigating the following hypotheses:

1) AI can be used for automated tumor delineation of HNC in a quality matching that of a nuclear medicine specialist.
2) It is possible to implement a generalized clinical artificial intelligence-based system for automated tumor delineation and collection of PET/CT-biomarkers from cancer patients in a data warehouse.
3) Combining PET/CT-biomarkers with microbiology, immunology, biochemistry and genetics can be used to improve predictions concerning mortality, recurrence and side-effects in HNC.
4) AI-systems in a data-warehouse environment used as clinical decisions support leads to decreased rates of mortality, recurrence and side-effects in HNC.

It is within the three-year scope of this grant to initiate investigation of the fourth hypothesis; however, the timeframe for this investigation, which will entail a clinical trial, will most likely go beyond the timeframe of a potential grant provided as a result of this application.

## Materials and methods

AI will be used for automated tumor delineation, collection of biomarkers and to develop improved prognostic models. This will initially be done for HNC patients (see Figure 1).

### Patients

Head and neck cancer patients scanned with 18F-FDG PET/CT at the Clinic for Clinical Physiology, Nuclear Medicine and PET at Rigshospitalet between 2014 and 2019 (approximately 400 cases per year), and who were treated with Radiotherapy, will be included in order to optimize and validate the segmentation techniques used for automated tumor delineation.

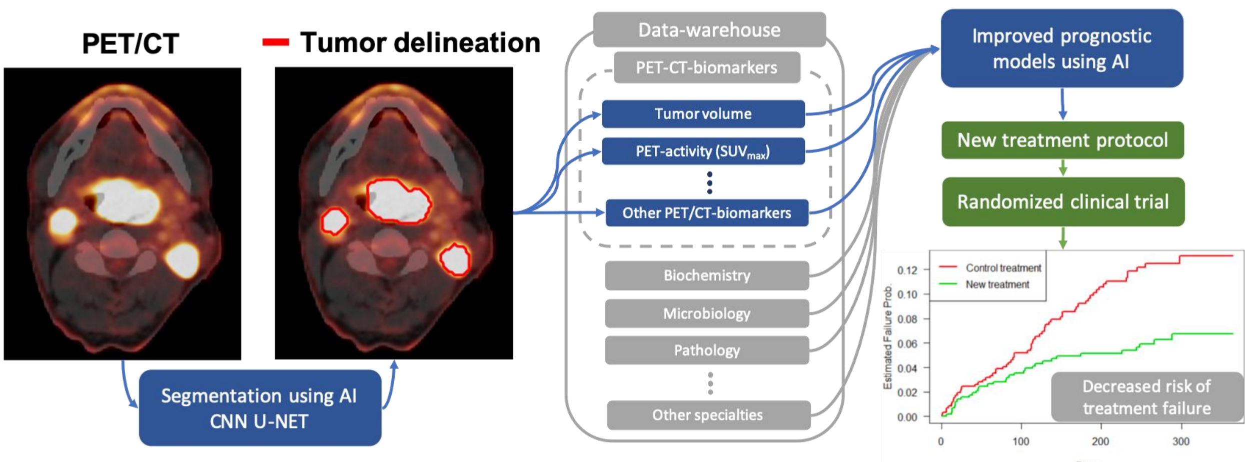


Figure 1: AI will be used in two phases of the project: 1) For automated delineations and collection of biomarkers and 2) for development of improved prognostic models using traditional statistical methods, such as Kaplan Meier analyses, and using AI methods such as deep learning neural networkds. The methods will be compared based on sensitivity and specificity. Resulting new treatment protocols will be tested in randomised clinical trials. An example of a delineated tumor, which we will produce automatically using AI, is presented in red on the PET/CT image Methods and biomarkers that will be developed, optimized or implemented as a part of this project are presented in blue. Parts of this projects that are planned and will be initiated, but which cannot be finished within the three year scope of this application are presented with green.

### Automated tumor delineation

To develop automated tumor delineation of high quality, PET/CT images and segmentation will be screened to ensure that all training data is performed at expert level. Selection bias will be attempted eliminated by stratifying included patients to ensure that the developed models will produce results, which are valid for a demographic as wide as possible. Stratification will in this regard be performed based on age, gender, race and weight. Training of the AI deep learning neural network for image segmentation will be done based on expert delineations which are currently done on all HNC PET/CT scans performed for radiotherapy planning.
The latest AI-methods described in the literature will be used to perform automatic tumor delineations and collection of biomarkers. A U-net will be trained using Keras software on a Tensorflow backend.[16], [39] The adaptation of the network for clinical use will be done using a structured optimization approach (grid search) of hyperparameters, including learning rate, drop-out, batch-normalization and choice of loss function. More complex new architectures, such as GAN-networks, will also be implemented and tested. Evaluation of the developed tools will be done by separating the data into a training, test and validation dataset. Cross-validation will be used to train the AI-algorithms on training and test data while the final performance will be reported based on the validation data set.
In addition to traditional AI evaluation parameters (such as root-mean-square-error) we will evaluate the techniques using parameters that have explicit clinical relevance, including the quality of tumor delineations measured by the DICE similarity coefficient, Hausdorff distance and the sensitivity and specificity to detection of sub-volumes.

## Prognostic modelling

Upon achievement of a satifactory tumor segmentation tool, selected biomarkers, such as SUVmax, SUVmean, MTV, TLG and SULpeak will be estimated and added to the data warehouse setup. These biomarkers will initially be combined with pathological and biochemical test results, as well as with patient journal information, and used to develop prognostic models for side-effects, recurrence and mortality. Prognostic model development including the novel PET/CT-biomarkers as predictors will be performed using traditional statistical methods, such as Kaplan Meier and Cox proportional hazard regression analysis, and compared to new prognostic models, which will be based on AI-techniques. These tecniques will include the machine learning methods variable selection in linear and logistic regression, decision trees, neural networks and ensemble methods, which will be used to identify the combinations of biomarkers across specialties, that best predict side-effects, recurrence and mortality.

## Perspectives

Our approach to design of clinical artificial intelligence solutions hold a potential to improve the course of cancer treatment for patients at our institution, nationally and internationally. In the current clinical setup, there is a risk for patients that aspects influencing diagnosis and treatment can be missed by physicians due to a lack of sharing of information between specialties. By collecting information and using artificial intelligence for analysis, we have a unique opportunity to improve treatment without exposing patients to tests beyond what is already performed today. In effect we will be able to utilize the large amount of information that already exists to the benefit of the patient.

Automated segmentation and collection of biomarkers can be used as clinical decision support, leading to more accurate treatment planning, improved prognostic and more timely and accurate diagnose. For instance, the methods can be used to predict which patient will be most sensitive to side-effects from chemo, immune-, surgical and radiotherapeutic treatment, hence systematically guiding the best choice of treatment for each patient. Such results will likely lead to a wider implementation of our AI techniques nationally and internationally.

Positive results in our pilot work with head and neck cancer patients will lead to extension of our methods to lung cancer patients and other patients with solid tumors. Given positive clinical validation of the techniques for these groups, our techniques can be extended to be used for the groups routinely. Our methods and results can also be extended to other diseases, such as multiple sclerosis and Alzheimers disease as well as to other specialties, including other radiological images, MRI images and classification of tumor tissue in pathology.

Ultimately, this is a step towards a better utilization of the enormous amount of information, which is already stored in out hospitals to create a clinical health care science paradigm shift where out all information about patients in a hospital contribute to a better treatment with fewer decreased side-effects, cases of recurrence, mortality and more healthy patients.

## Ethical considerations

Our research can give rise to clinical trials, as the developed prognostic models may have an influence on treatment protocols. Clinical trials will be conducted after approval by the regional scientific ethics committee. Patient will only be included in the studies after providing oral consent and signing and written consent forms. The project will be conducted in a scientifically sound manner, according to the latest version of the Helsinki declaration and in accordance with common standards for responsible conduct of research.

## Implementation and reduction of risk

The project will largely be completed by means of a biomedical engineering ph.d-student over a period of four years with experience in medical image analysis, clinical oncology, and machine learning and by guidance of experienced technical and medical researchers at our department. The research group is embedded in a clinical environment, ensuring that the project results will be further developed and implemented to create value for the benefit of cancer patients in Denmark and internationally. The department for Clinical Physiology, Nuclear Medicine and PET at Rigshospitalet has previously implemented deep learning AI techniques for attenuation correction of PET, computation of synthetic CT based on MR, delineation of lesions in multiple sclerosis and noise reduction for decreased PET scan time. Hence there is a considerable expertise at the clinic, which increases the probability of a positive outcome of this project. Successful tumor delineations in HNC of clinical expert quality and data sharing across specialties will be implemented during the timeframe of this project, creating tangible value for the Danish health care system within the duration of a potential grant from the Independent Research Fund Denmark based on this application.

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