Lung cancer is one of the major public health problems worldwide, being responsible for one-fifth of cancer-related deaths. The majority of lung cancer cases is diagnosed at advanced stages and have unfavorable prognosis (the average 5-year survival of about 10-15%). However, in the case of the disease detected at early stages, the prognosis is much better (the average 5-year survival varies between 65 and 85%). Thus, in addition to primary prevention (i.e., tobacco smoking control), screening for the early detection of lung cancer was proposed as a promising strategy to reduce lung cancer mortality. Several screening tools have been investigated during past decades, but only one – the low-dose computed tomography (LD-CT), has application in clinical practice. However, due to low specificity of LD-CT, the vast majority of patients with screen-detected chest abnormalities are subjected to further expensive and potentially harmful diagnostic procedures, such as transthoracic or bronchoscopic biopsy or surgery (it is estimated that 75% of patients unnecessarily underwent diagnostic work-up, including 25% subjected to invasive procedures). To reduce over-diagnosis and decrease the costs, there is an urgent need for clinical tests supporting CT-based screening for the detection of lung cancer. Such tests could either pre-select individuals for LD-CT examination or discriminate between benign and malignant chest abnormalities detected by LD-CT.

The overall response of human's organism to pathological conditions is mirrored in different molecular fractions of body fluids. Blood is a particularly valuable source of molecular information on disease-related processes, with many actual and perspective applications as a "liquid biopsy" of cancer. Several different components of blood, including circulating tumor cells, circulating DNA, micro RNA, autoantibodies and specific serum/plasma proteins, have been analyzed as potential (early) lung cancer biomarkers. Among the biomarker candidates proposed for detection and diagnosis of lung cancer are multicomponent panels of serum proteins or micro RNAs, yet only a few of them have been tested for diagnosis of the early stage cancer. Monitoring of cancer-related metabolites in blood is an emerging approach in the detection and diagnosis of different malignancies. Several studies demonstrated that profiling of serum or plasma samples using nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS) can deliver metabolomics signatures discriminating patients with lung cancer from healthy individuals or patients with non-malignant lung diseases Exosomes circulating in blood constitute an emerging topic in the field of liquid biopsy of cancer, which is a promising and valuable source of biomarkers characterizing the disease. Radiomics is a strategy based on the extraction of many quantitative features from the computed tomography (CT) image for the improved differentiation of lung malformations.

The current proposal concerns the possibility to estimate the risk of lung cancer based on a novel combination of molecular and radiomics features assessed in the early "pre-clinical/symptomless" stages of the disease. We suppose that disease-related features of cellular metabolism could be detected in the serum of individuals with a low advanced lung cancer. Moreover, we presume that exosomes isolated from serum of such individuals contain molecules (metabolites, proteins and miRNA species) characteristic for the systemic response of patient's body to the disease. Furthermore, we assume that radiomics signatures established due to the computation-assisted quantitative analysis of LD-CT images of the chest allow for more effective detection and better characterization of lung nodules. Hence, the general hypothesis driving this proposal states that the combination of a serum-based signature of the molecular phenotype of disorder with a radiomics signature of lung nodules detected by the imaging approach would allow building a joint classification model for better stratification of cancer risk during screening for the early detection of lung cancer.

Four major specific objectives of the proposal are planned: (1) to perform analysis of the serum metabolite profile and to identify a molecular (metabolomics) signature of early lung cancer; (2) to perform analysis of serum exosomes and to identify in their molecular cargo of components (metabolites, proteins, and miRNA) associated with a disease-related phenotype; (3) to create relevant algorithms for LD-CT data analysis and to establish radiomics features of different types of lung nodules; (4) to build, test and validate a joint classification model of early lung cancer based on the combination of molecular phenotype of serum signature and radiomics features of lung nodules detected by LD-CT.

We expect that the project will deliver original knowledge expanding our understanding of lung cancer. Moreover, the classification model that join parameters of a systemic response of patient's body to the disease (i.e., metabolomics/molecular signature of serum) and physical parameters of local CT-detected lung nodules (i.e., radiomics signature of lung cancer) might have important implications for future applications related to early detection of lung cancer during screening programs based on LD-CD and biomarker assessment.