LUCIA Understanding Lung Cancer related risk factors and their Impact

Horizon Europe Grant Agreement Number: 101096473

Deliverable Number	D4.4
Deliverable Title	Clinical protocol and regulatory authorization report: General population Screening
Due date of deliverable	31.01.2024
Actual Submission Date	28.01.2024
Responsible partner	Biobizkaia Health Research Institute (BB)
Contributors	Clinical Partners
Revision (draft, 1, 2, ...)	1.0
Dissemination Level	PU - Public

Start Date of the project: January 1, 2023
Duration: 48 months

Document information

Status	Revision date	Authors
1st draft	12.01.2024	Jon Eneko Idoyaga Uribarrena
2nd draft	22.01.2024	Internal review by Clara Frick (DKFZ)
Final version	22.01.2024	Jon Eneko Idoyaga Uribarrena

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Contents

1. Executive summary

This deliverable has been conceived in the frame of T4.2 “Clinical protocols and requirements”, which is devoted to the organization of the assessment methodology that will be implemented during the development of each use-case at different level after risk stratification of citizens and clinical scenario. All the designs will be based on feedbacks and results after of tasks developed in WP3 and WP5. The following actions will be deployed:

- developing and agreeing on the sampling plan;
- choosing and testing measurement instruments;
- choosing the early diagnosis clinical pathways;
- choosing the diagnosis workflow; and
- planning the data collection and the validation protocols.

After the protocol design (which has already been finalized), all the authorizations required by the regulatory authorities will be obtained.

This deliverable provides the essential regulatory and research documents for the beginning and development of Task 4.3: “General population screening” under which the prospective clinical study will start recruiting participants and gathering data for the LUCIA project.

The content of this deliverable summarizes the clinical protocol for the cohort study in the general population screening and the regulatory authorizations that must be obtained before the enrollment of the first participant in the study.

This deliverable includes the following information:

- Final version of the study protocols of each clinical site as sent to each one of their respective ethics committees.
- Regulatory authorizations required for the enrolment of the first study participant

The consortium partners have finalized and agreed on the common prospective clinical protocol, which ensures we reach the highest standards of quality and clinical and scientific relevance. The protocols have already been submitted to each one of the Ethics Committees for its approval request in December 2023.

We foresee to obtain the approval of the Ethics Committees in the coming months and start the recruitment of the volunteers that will participate in the prospective clinical study as soon as we get those approvals.

Since the approval has not been obtained yet, we provide in this document the documents of Request for Evaluation of research projects by the Ethics Committees of each clinical site until we obtain the approvals. Once we get them, we will provide also these regulatory authorizations.

2. General Population Screening prospective protocol

In this section, we provide the clinical protocols as each one of the clinical sites have sent them to their respective ethics committees for their approval.

The 4 clinical sites that will take part in the General Population Screening prospective clinical study are:

- **Andalusia**: Servicio Andaluz de Salud (SAS)
- **Basque Country**: Osakidetza – Servicio Vasco de Salud
- **Belgium**: Centre Hospitalier Universitaire De Liege
- **Latvia**: Latvijas Universitate (Centre for Tuberculosis and Lung Diseases of Riga East University Hospital)

Even though, at the core, the protocols for the prospective clinical study are mainly the same, each clinical site has included slight modifications to the protocol to adapt it to the capabilities and clinical practice of their respective institutions and health care systems.

These modifications do not entail any risk to the objectives, vision and ambition of the LUCIA project. Furthermore, they ensure that the study is manageable and adaptable to the healthcare systems of the 4 European regions (Liège, in Belgium; Riga, in Latvia and the Basque Country and Andalusia, in Spain) that take part in the clinical study.

Below, we provide the common text for the General Population Screening prospective protocol in which we address the slight differences applied in each clinical site. To consult the full text of the versions of the "Clinical Management and Study Plan" sections included in each one of the protocols sent to the Ethics Committees, please, go to the annexes section.

1. OBJECTIVES AND PURPOSE OF THE PROJECT

1.1. Hypothesis

Determining eligibility for screening by individualized risk (based on age, more detailed smoking history, occupational exposure and other risk factors such as ethnicity and family history of lung cancer) and the development and validation of lung cancer risk predictive models can improve screening efficiency and reduce LC morbi-mortality.

These models will allow implementing new clinical pathways and diagnosis workflow to ensure fast diagnosis and confirmation, including subtype of lung cancer classification.

According to the principles set out by Wilson and Jungner in 1968, a screening program should be based on a pathology that can be improved through the use of population screening. In addition, screening tests must meet a series of criteria, such as: the test must be well accepted; costs must be balanced with benefits; the risks, both physical and psychological, should be less than the benefits and there must be an adequate test to detect it in the initial stage; among others. Nowadays, another important limitation in the implementation of population screening programs for lung cancer are the risks of radiation and the high cost of low-dose CT as a screening test. This is why LUCIA aims to develop and validate new tests, based on new technologies, which will allow for the implementation of more efficient, acceptable and equitable population screening programs in the early future.

1.2. Main Objective

LUCIA aims to develop prediction models for early diagnosis of lung cancer based on the identification of risk factors and a deeper cellular understanding, by the register of real-world data; with risk assessment tools, noninvasive screening devices and omics analysis.

1.3. Secondary Objectives

- To analyse and validate the impact of real-world data to identify risk factor models related with the development of lung cancer
- To identify cohorts based on levels of risk of developing lung cancer
- To evaluate the risk assessment model for predicting lung cancer in non-smokers
- To analyse and validate new risk factor assessment tools and AI models to be implemented in lung cancer screening programs
- To develop a deeper cellular understanding to evaluate potential changes in the diagnosis workflow, including the subtype of LC classification

- To analyse all strategies in different epidemiological and sociodemographic context to carry out an effective screening
- To develop an advanced polygenetic scoring combined with biomarker inputs for lung cancer
- To analyse the diagnostic accuracy of new screening tools for early detection in lung cancer
- To describe the socio-economic structure of the trial participants and assess the representativeness of individuals with lower socioeconomic backgrounds and gender balance
- To further evaluate sex and gender differences in lung cancer risk and screening effectiveness

2. METHODOLOGY

2.1. Study Design

- This is an analytical observational, longitudinal, multicenter cohort study.

2.2. Study Period

- This study estimates a recruitment period of 18 months.
- The total duration of the study is estimated for 36 months, including the time necessary after the recruitment of the last subject for closing and editing the database, data analysis and preparation of the final study report.

2.3. Study Population

- Adult subjects (40 years old or higher), smokers and non-smokers, both women and men who have the capacity to comply with the study follow-up and sign the informed consent, will be recruited from “Servicio Andaluz de Salud” (SAS), “Osakidetza Servicio Vasco de Salud” (OSA), “Centre Hospitalier Universitaire de Liège” (CHUL) and “Centre for Tuberculosis and Lung Diseases (CTLD) of Riga East University Hospital (REUH)”.

2.4. Selection Criteria

2.4.1. Inclusion Criteria (for the 3 phases)

- Subjects aged between 40 and 80 years
- Both genders, of which at least 37% must be women to ensure representativeness

- Willingness and ability to comply with scheduled visits, laboratory tests, and other trial procedures
- Written informed consent obtained prior to performing any protocol-related procedures.

2.4.2. Exclusion Criteria

- Subjects under 40 years of age
- Unable to be followed-up for at least 2-years or complete the study
- Subjects that do not sign the informed consent
- Current or prior history of lung cancer
- History of neoplasia in the previous 5 years except non-melanoma skin cancer
- Moderate-severe comorbidities that prevent completion of a diagnostic study in the event of findings suggestive of lung neoplasia (by means of the investigator's clinical judgment) or surgical intervention (< 6 months) if not previously confirmed by cytohistology.
- Vulnerable subjects: severe psychiatric comorbidity, adults under guardianship or deprived of liberty
- Pregnant women

2.5. Randomization Process

All participants who have signed the informed consent will be assigned a unique identifier and receive the baseline screening.

There will not be any randomization process. The whole study population will be assessed and followed up.

3. SAMPLE DETERMINATION AND SAMPLING

To achieve a precision of 1.00% in estimating a proportion using a two-sided Normal asymptotic confidence interval at 95.00%, assuming that the proportion is 8.60% (GLOBOCAN 2020; http://gco.iarc.fr) and effect size of 0.2, it will be necessary to include 5,674 volunteers in the study. Taking into account that the expected percentage of dropouts is 10.00%, it would be necessary to recruit 6.160 volunteers in the study.

We will ensure that at least 37% of the subjects included in the study are women and that 20% of the whole population in the study are non-smokers or reduced smokers (subjects that have smoked less than 100 cigarettes in their life).

This will lead to a minimum of 2,279 women and 1,232 non-smokers or reduced smokers (NSRS).

6 months after the beginning of the project an interim analysis of the recruited patients will be carried out to verify the heterogeneity of the sample, to ensure that we comply with the representativeness of each group in the study and to reach the statistical power necessary to achieve the objectives of LUCIA. If the sample size needs to be increased, new volunteers will be recruited from pneumology consultations of the clinical partners.

Also, if the minimum percentage of subject per group is not achieved, the recruitment will follow in the misrepresented group until the balance is restored.

During this interim analysis, during phase 1 (wide population screening), if the minimum number of subjects is not achieved, we will include patients with findings of indeterminate pulmonary nodules in specialized consultation who meet the rest of the inclusion criteria.

Based on the NLST and NELSON trials, the prevalence of the general population at high risk of developing lung cancer could be between 6.6-8.9%. LUCIA intends to establish models that identify the population at high risk, a subsidiary of population screening for lung cancer, with greater precision. Based on the contrasted evidence in the literature, it would be estimated that the follow-up cohort in precision screening could be around 300-400 volunteers. Through the implementation of new technologies to be validated in LUCIA, the aim is to improve the early diagnosis of lung cancer. Estimating an improvement from 25% (current figures for diagnosis in early stages according to the American Cancer Society) to 65%, the population that would have to follow to reach a power of 90% and a level of significance of 1.0% would need to have a sample size of 210 volunteers. On the other hand, based on the risk of general population in developing lung cancer, we can estimate that more than 300 patients will be followed with the diagnosis of pulmonary nodules or LC, taking into account the prevalence of these pathologies all over Europe. A total of 1,000 will be targeted and reached by extending the recruitment to include also patients with new diagnosis of pulmonary nodules or LC, outside the screening phases, to ensure sufficient data for AI modelling of pathology and risk factors.

In this phase, in order to reach the objective of recruited participants, and to reach the number needed of patients with the diagnosis of pulmonary nodules or LC, if necessary these patients will be included from consultancies of Neumology or Oncology settings.

Finally, to ensure that we comply we the project's goal, during phase 3 (diagnosis) we will include both CT screened patients that are referred for follow up scan because of the

presence of Indeterminate Pulmonary Nodules (IPN) and subjects identified Lung Cancer following their baseline scan.

4. SCIENTIFIC VARIABLES

4.1. Main Variable

The main variable is the presence of pulmonary nodules and/or Lung Cancer diagnosis identified by tomographic tests.

4.2. Secondary Variables

- Clinical Variables:
  - Sociodemographic data: Age, Gender, ethnicity, socioeconomic factors, deprivation index, education level.
  - Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
  - Spirometry result.
  - Medical record: Family history of lung cancer or other types of cancer, emphysema/ COPD (+GOLD classification)/ asthma, Interstitial Lung Disease (interstitial patterns), bronchiectasis, arterial hypertension, dyslipidemia, previous acute myocardial infarction, vasculopathies and chronic treatment.
  - Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).
- Analytical variables (General overview of potential markers) combining mandatory and nice to have biological markers collected either prospectively or through standard of care (SOC):
  - General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Transferrin Index, Cholesterol, transferrin, phosphate, calcium
  - Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
  - Kidney profile: urea, Creatinine, Sodium, potassium, Urate
  - Tumor markers: CEA, CA125, CYFRA 21.1, NSE
  - General haematology: blood count, erythrocyte sedimentation rate
  - Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time

- Exploratory Omics markers (subgroup: n=2350):
  - Dedicated blood samples will be specifically performed for a large Omics analysis.
- Questionnaires:
  - Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence test and EuroQoL.
- Geo-location and open data
- Device data:
  - Breath Analyzer (BAN): Biomarkers and signals from breath
  - Wide-biomarker-spectrum Multi-Use Sensing Patch (WBSP): Biomarkers and signals from skin
  - Spectrometry-on-Card (SPOC): Biomarkers and signals from blood samples.
- Tumor pathology:
  - Tumor biopsy result
  - Liquid biopsy result
- Lung CT scan description

5. CLINICAL MANAGEMENT AND STUDY PLAN

PHASE 1 study: General population screening: *Identify citizens with low to moderate risk of LC according to the developed risk factor assessment tools, suitable for further screening using low-cost devices in community-based settings or in centralized screening facilities*

VISIT 1 - Baseline

Clinicians from the different clinical centers will identify possible participants from their consultations. These participants will be both smokers and never smokers & reduced smokers with low to moderate risk of Lung Cancer who meet the criteria generated by risk factor assessment tools.

Recruitment will ensure only eligible participants are included so that relevant and high-quality data is collected. Targets will be set to ensure research activities are delivered on time. All possible measures will be taken to ensure there is no discrimination or harms from the recruitment, exclusion or inclusion process.

On the first day of visit 1 or baseline, the principal investigators and their team of collaborators will review the eligibility of patients who meet the inclusion criteria and none of the exclusion criteria, established in sections 4.4.1 and 4.4.2.

Recruitment will be carried out by the main investigator and/or the co-investigators authorized to do so at the General Practitioner and/or pneumologist's consultation. The researcher will proceed to inform the selected patients about the possibility of participating in the clinical trial by explaining them what their participation will consist of through the Patient Information Sheet and the Informed Consent. The participants will be able to ask all the questions they deem appropriate in order to clarify all their doubts and will take the time they consider necessary to decide.

If the patient wishes to participate in the study, they will sign the Informed Consent and a code will be assigned to guaranty the pseudoanonymization of the patient and included in the participant's electronic health record (EHR).

The code will be as it goes:

LUCIA-XX-####

Being:

- **XX**: the code of the site where the patient has been recruited (AN for Andalusia, BC for Basque Country, LI for Liège and RI for Riga)
- **####**: the number of patient recruited (consecutive numbers in order of recruitment from 0001 to 1,000)

During this first visit, the principal investigator and/or their collaborators will access the EHR of each patient and will record the clinical data:

- Sociodemographic data: Age, Gender, Ethnicity, socioeconomic factors, deprivation index, education level.
- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
- Spirometry result **(not performed in Latvia)**
- Medical record: Family history of lung cancer or other types of cancer, emphysema/ COPD (+ GOLD classification)/ asthma, Interstitial Lung Disease (interstitial patterns), bronchiectasis, arterial hypertension, dyslipidemia, previous acute myocardial infarction, vasculopathies and chronic treatment.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence test and EuroQoL.
- Geo-location

All clinical sites will perform or use a standard of care (SOC) common blood test that will be enriched in each one of the sites as follows:

- **Andalusian Clinical Site**: Investigators will collect a blood sample of the participants for its analysis, including:
  - General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Cholesterol, transferrin, phosphate, calcium
  - Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
  - Kidney profile: urea, Creatinine, Sodium, potassium, Urate
  - General haematology: blood count, erythrocyte sedimentation rate
  - Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
  - Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).
- **Basque Country Clinical Site**: Investigators will collect a blood sample of the participants for its analysis, including:
  - General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Transferrin Index, Cholesterol, transferrin, phosphate, calcium
  - Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
  - Kidney profile: urea, Creatinine, Sodium, potassium, Urate
  - Tumor markers: CEA, CA125, CYFRA 21.1, NSE
  - General haematology: blood count, erythrocyte sedimentation rate
  - Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
  - Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and

epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

- **Belgian Clinical Site**: Investigators will use data gathered through SOC, including but not limiting to variables (General overview of potential markers) combining mandatory and nice to have biological markers collected through SOC:
  - General Biochemistry: C reactive protein, Proteins, Chloride
  - Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
  - Kidney profile: Creatinine, Sodium, potassium, Urate
  - General haematology: blood count
  - Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of patients enrollment and management of these blood samples are describe in section 8).
- **Latvian Clinical Site**: Investigators will use data gathered through SOC, including but not limiting to variables (General overview of potential markers) combining mandatory and nice to have biological markers collected through SOC:
  - Glucose, C reactive protein, Proteins, Albumin, Calcium
  - Hepatic profile: GPT, GGT, Bilirubin, Alkaline phosphatase
  - Kidney profile: urea, Creatinine, Sodium, potassium,
  - General haematology: blood count, erythrocyte sedimentation rate
  - Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of patients enrollment and management of these blood samples are describe in section 8).

If abnormal values are observed after performing the blood analysis, the researcher in charge of the subject involved in the study will handle the situation according to usual clinical practice.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

All these data will be entered in the Case Report Form (CRF) of the study developed by Bilbomática.

- **Andalusian Clinical Site**: No CT scan will be performed in this phase.
- **Basque Country Clinical Site**: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.
- **Belgian Clinical Site**: If an acceptable LDCT or CT image is available based on patient medical file from less than 12 months, it will be used for the study in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.
- **Latvian Clinical Site**: No CT scan will be performed.

Based on the assessment carried out by the results of the LDCT (only for Basque Country and Belgium), the devices (individuals who show positive or uncertain results) and by established risk factor models, subjects will:

- Continue in **Phase 1: Wide population Screening** if low-moderate risk of lung cancer is assigned.
- Be referred to **Phase 2: Precision Screening** and included within polygenetic scoring analysis if high risk of lung cancer is assigned.
- Be referred to **Phase 3: Diagnosis** if by results of LDCT lung cancer or Indeterminate Pulmonary Nodules (IPN) are found.

Follow up visit 2 (6 months ± 30 days)

6 months after the beginning of the project an interim analysis of the recruited patients will be carried out to verify the heterogeneity of the sample and to ensure that we comply with the representativeness of each group in the study.

If the minimum percentage of subject per group is not achieved, the recruitment will follow in the misrepresented group until the balance is restored.

This visit will be performed remotely.

During this visit, the following information will be recorded:

- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

Follow up visit 3 (12 months ± 2 months)

During the follow up visits (12 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
- Spirometry result **(not performed in Latvia)**.
- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence and EuroQoL.

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite

- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

All these data will be entered in the Case Report Form (CRF) of the study and in the app developed by Bilbomática.

Final visit (24 months ± 2 months)

During the last visit (24 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
- Spirometry result **(not performed in Latvia)**.
- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist and EuroQoL.

All these data will be entered in the Case Report Form (CRF) of the study.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

- **Andalusian Clinical Site**: No CT scan will be performed.
- **Basque Country Clinical Site**: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project.
- **Belgian Clinical Site**: If an acceptable LDCT or CT image is available through SOC during visit follow up from less than 12 months, it will be used for the study in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project.
- **Latvian Clinical Site**: No CT scan will be performed.

Flow Chart of the study:

		PATIENT PHASE 1*			
		Baseline	Follow-up		
	VISIT	1	2#	3	4
	MONTH	0	6	12	24
	TIME WINDOW (days)	-	30	60	60
Informed Consent Form Signature		X			
CLINICAL & SOCIODEMOGRAPHIC DATA	Sociodemographic data (A)	X			
	Physical exploration (B)	X		X	X
	Medical record (C)	X	X	X	X
	Exposure to harmful agents (D)	X	X	X	X
	QoL Questionnaires (E)	X		X	X
	Geo-location	X			
IMAGING	CT Scan ***	X			X
BIOLOGICAL**	General biochemistry (F)	X			
	Hepatic profile (G)	X			
	Kidney profile (H)	X			
	Tumor markers (I)	X			
	General hematology (J)	X			
	Hemostasis (K)	X			
GENETIC TESTING	Omics analysis based on blood samples	X			
OTHER	Liquid biopsy				
NEW DEVICES	Breath Analyzer (BAN) (L)	X			X
	Spectrometry on Card (SPOC) (M)	X			X
	Wide Spectrum Biomarker Sensing Patch (WBSP) (N)				

GUIDE SYMPTOMS	Cough		X	X	
	Coughing up blood or rust-colored sputum		X	X	
	Chest pain		X	X	
	Hoarseness		X	X	
	Loss of appetite		X	X	
	Unexplained weight loss		X	X	
	Shortness of breath		X	X	
	Feeling tired or weak		X	X	
	Infections (bronchitis, pneumonia, …)		X	X	
	New onset of wheezing		X	X	

*Patients in phase 1 can be include in phase 2/3 after 6 months interim analysis.

***CT Scan:

- Andalusian Clinical Site: No CT scan will be performed.
- Basque Country Clinical Site: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.
- Belgian Clinical Site: In order to optimize the resources of each health system, patients may also be included in the study by chest CT performed through the standard of care (both low dose or high resolution, image obtained less than 12 months ago). At all times, stratified sampling will be carried out ensuring the heterogeneity of the samples and the selection criteria. Patients who have been referred for chest CT for suspected lung cancer will not be included.
- Latvian Clinical Site: No CT scan will be performed.

**** Biological data: In order to optimize the resources, biological data will be gathered through SOC procedures.

#Remote visit

6. SAMPLE HANDLING

6.1 SAMPLE REQUIREMENTS

- The sample requirements to perform WGS with Oxford Nanopore Technologies (ONT) are: 6-10µg of high molecular weight (HMW) DNA for each flow cell to be processed.
- High-quality, high-molecular-weight genomic DNA is imperative for obtaining long read lengths and optimal sequencing performance.

General guidelines for handling high-molecular-weight DNA

In general, the following precautions need to be taken when handling DNA:

- Avoid over drying of genomic DNA. Allow the DNA to air dry. Do not heat when drying in a speed-vac.
- DNA should be eluted in neutral, buffered solution (e.g., 10 mM Tris Acetate or Tris-HCl, pH 8) and stored in TE (10 mM Tris, pH 8, 1mM EDTA) *. Avoid eluting in RNAse-free H_2O or unbuffered solutions.
- Please provide a 10ul aliquot of the buffer employed for DNA elution.
- PCR products should be clean amplicons.
- If gel purification is required, avoid using ethidium/UV based visualization methods. One alternative is to use SYBR® Safe (Invitrogen) and visualize with blue light.
- To resuspend the DNA, carefully invert the tube several times after adding buffer and/or tap the tube gently. Alternatively, allow the DNA to stand in buffer overnight at 25°C.
- Overheating can introduce DNA damage. Inactivate DNAase as recommended by the vendor kit. It is best to avoid heat inactivation when possible. An alternative is AMPure® purification.
- Avoid small opening tips and vortexing. Genomic DNA is physically fragile and shears by pipetting and vortexing
- DNA storage conditions: 4°C (short-term); –20°C / –80°C (long-term).
- Repeated freezing and thawing of genomic DNA should be avoided

*Note: EDTA must be removed prior to library preparation. This can be achieved during the initial AMPure purification.

Important measures impacting DNA quality

To maximize read length and quality, it is essential that the DNA sample:

- Is double-stranded
- Has not been exposed to high temperatures (e.g.,>65ºC for 1h) or extreme pH (<6 or >9)
- Has an OD260/OD280 ratio of 1.8 to 1.9.
- Has an OD260/OD230 ratio of 2.0-2.2.
- Does not contain insoluble material or RNA contamination
- Does not contain denaturants (e.g., guanidinium salts or phenol) or detergents (e.g., SDS or Triton-X100).
- Does not contain carryover contamination from the original organism/tissue (e.g., heme, humic acid, polyphenols, etc.)

DNA sample quality assessment:

A thorough DNA quality check is required prior to submitting DNA. The following recommendations to ascertain DNA integrity, purity, and concentration are recommended:

1) Gel images of DNA sample: Genomic DNA integrity can be assessed by agarose gel electrophoresis; however, optimal fragment size assessment should be done by pulsed-field gel analysis. Expected average fragment size is >80 kb.
2) Purity of DNA sample: DNA purity should be determined by using the NanoDrop® instrument. Readings of both A260:A280 and A260:A230 need to be obtained:
    a. 260/280: The ratio of absorbance at 260 nm and 280 nm is used to assess the purity of DNA. A ratio of ~1.8 is generally accepted as “pure” for DNA, but is dependent on the nucleotide composition of the submitted sample. A low A260/A280 ratio may indicate the presence of protein, phenol or other contaminants that absorb strongly at or near 280nm. Sometimes it may be caused by a very low concentration of nucleic acid. High 260/280 ratios are not indicative of an issue, value >1.9 usually indicates repetition of an RNase digestion.
    b. 260/230: The 260/230 ratio provides a secondary measurement of DNA purity to make inferences about the quality of sample extraction. Expected 260/230 values are commonly in the range of 2.0-2.2. Abnormal 260/230 values may indicate a problem with the sample extraction procedure. The Protein LoBind tubes will improve UV 260/230 ratios by up to 0.1 – 0.4 by preventing carryover of contaminants stuck to the tube surfaces.

In addition to the Nanodrop ratios it was found critical that the ratio of DNA concentrations measured on the Qubit and Nanodrop instruments respectively should be 1:1.5. This ratio indicates that most DNA molecules are double-stranded and that no other molecules (e.g., RNA) are present that absorb at 260 nm (Schalamun et al., 2018).

3) Concentration of DNA sample:

It is critical to determine the concentration of the double-stranded DNA, since only double-stranded DNA will be converted into sequencing templates. RNA, dNTPs, and single-stranded DNA included in the concentration measurement will skew the concentration reading. Therefore, it is highly recommended to use the PicoGreen® assay or a Qubit® fluorimeter for quantitation purposes. Requested minimal input mass for one GridION or PromethION flowcell run, as measured by Qubit, is 6 µg depending on the expected MW.

Accepted Buffers

- DNA can be dissolved in Tris buffer (e.g., 10 mM Tris, pH 7.0 – pH 8.0). Do not use nuclease-free water as this is insufficient for long-term DNA stabilization. Only for long-term storage of high molecular weight (HMW) gDNA we recommend the use of TE buffer, however, as this is not compatible with some enzymatic reactions (Mg++ dependent) it should not be used as the first-choice buffer.

Options for DNA Extraction from blood cells:

a) aQiagen MagAttract® HMW kit (100-200 kb) – (special equipment needed)
b) Qiagen Genomic-tip kit (50-100 kb) – Highly recommended for HMW DNA and mtDNA extraction or for extraction of bacterial DNA
c) Qiamp DNA kit (50 kb) was particularly tested for whole blood DNA extraction where mtDNA was well retained
d) Qiagen Gentra Puregene kit (100-200 kb) – Not recommended for the mtDNA extraction and bacterial extractions
e) Phenol-chloroform extraction - Ensure phenol is fresh and not oxidized; use within three months of opening of reagent bottle.

http://cshprotocols.cshlp.org/content/2006/1/pdb.prot4455.long. DNA extraction protocol adapted from Molecular Cloning by Sambrook and Russell

(third edition). Chapter 6 protocol 1- Josh Quick, Ultra-long read sequencing protocol for RAD004 Version 3

6.2 LABELLING AND PACKAGING INSTRUCTIONS

- You'll receive 500ul tubes with lateral 1D barcode and 2D barcode in the bottom in a 96-rack.
- Tubes can be handled manually or with compatible automated platforms 0.
- Do not overfill tubes with more than 500ul.
- Blue capped tubes are to be used for DNA samples
- Tubes are numerically ordered but not always consecutive, by columns. CNAG will provide the clinical sites with an excel file with all barcode's IDs and initial rack position.
- Do not alter the labels in anyway: Tube labels show a unique CNAG sample barcode (format: 3 letters, 5 numbers). Rack label shows the project name and date of barcodes submission, and plate order in case submission contains more than one rack (1/n, 2/n, … n/n).
- Never apply Parafilm around the tubes cap, they have an anti-leakage system in the cap or paste any additional label on tubes.
- For the shipment, ensure racks are well closed to avoid tubes to be scattered in a box or directly in dry ice.
- DNA samples should be shipped refrigerated at 4ºC (with blue ice/cooling blocks)

6.3 SAMPLE DELIVERY INSTRUCTIONS

- Check that all the samples conform to the requirements and that they are prepared and packed according to the guidelines given above.
- Contact project management (projectmanager@cnag.crg.eu) to open a new subproject in the CNAG's LIMS (Laboratory Information Management System).
- CNAG biorepository will contact the clinical sites to provide the barcoded tubes and an URL link for data submission. Use only the material provided by CNAG for sample shipment.
- Submit sample data BEFORE sample shipment. Notify by email to CNAG Biorepository (lidia.agueda@cnag.crg.eu or ana.gonzalez@cnag.crg.eu) the date of delivery and provide the shipment tracking information whenever possible.
- CNAG barcodes that appear on the submission site can be used in different shipment batches. Select and submit the barcodes used for each shipment. Next time the URL is used it will only display the unused barcodes.
- Parcel reception times: send parcels preferably at the beginning of the week

Monday to Friday 8-12h.

No reception on Saturday, Sunday and local bank holidays

Shipment address:

ATT. Lídia Agueda, PhD / Ana González, PhD
Centre Nacional de Anàlisi Genòmica (CNAG)
Parc Científic de Barcelona – Torre I
C/Baldiri i Reixac, 4
Barcelona 08028 – Spain

- For non-EU shipments: additional documentation will be requested by the custom authorities. CNAG has to gather several documents and handle it to Spanish Customs, once the import is authorized, CNAG contacts the collaborator to define shipment date.

6.4 BLOOD SAMPLE preparation for SPOC analysis.

1. Approximately 1200 (1000 samples and additional blank tube for each sampling day) EDTA vacutainers from same batch production should be prepared for the experiments.
2. Exactly 3 ml blood sample will be collected in EDTA vacutainers.
3. After collection, the blood samples will be stored in a refrigerator (2-6 °C) until analysis.
4. Every sampling day, 1 empty tube should be added to the analysis as a controlling blank sample.
5. Blood samples should be introduced and analyzed in SPOC system up to 3 days from sampling.
6. Before sampling the headspace of blood sample vacutainers, the blood tubes should be heated to 40 °C (in a lab water bath or hot plate) for 30 minutes and directly then introduced to SPOC device for analysis.
7. After analysis is completed, samples can be discarded according to hospital regulations

7. INVESTIGATIONAL PRODUCT

The following devices will be used and tested in the study:

7.1 Breath Analyser: The NaNose Sensor consists of an innovative smart sensor array, that measure Volatile Organic Compounds (VOCs) emitted in the exhaled breath. NaNose Sensors are embedded in DiaNose system. DiaNose system consists of innovative smart sensors that measure VOCs emitted in the exhaled breath.

- DiaNose System Description: The DiaNose units consist of the following elements (Figure 1):

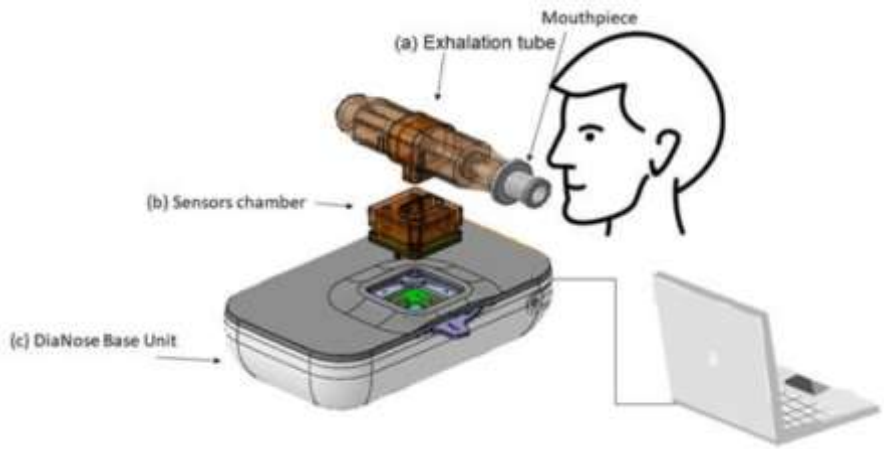


Figure 1: elements of the DiaNose unit

a) Breath collection unit: The tested subject exhales through the tube and withdraws after a complete, single exhalation. The exhalation is through of-the-shelf mouthpiece with saliva trap and a one-way check valve that eliminates the possibility of a subject inhaling air back from the mouthpiece. The last 40 ml of the exhaled breath gas, the end-tidal fraction, remains trapped in the tube. The exhalation into the tube is performed while it is dis-connected from the main device. This unit is for single use.

b) Sensors Chamber: This unit contains the Nanose sensors. The trapped breathed air in the breath collection unit is transferred through the sensors chamber by a pump upon the 2 units connection, as described below. The sensors chamber is a replaceable unit. Instruction regarding replacement frequency will be supplied with the units.

c) DiaNose Base Unit: a multi-use unit containing the sensors' signals measurement electronic card and a pump that transfers the exhalation sample from the breath collection unit to the sensors chamber. The Sensor Reading Unit is connected to a Laptop by a USB cable.

d) Laptop: Laptop is used to activate and save the test measurements

– NaNose Sensors: Main Device Components

DiaNose system consists of innovative smart sensors that measure VOCs emitted in the exhaled breath. The sensors, developed by Prof Haick group at the Technion, and further by NaNose medical, are based a chemiresistor platform. They are composed of thin films of chemically capped Gold Nano Particles (GNPs) between adjacent printed microelectrodes (Figure). The GNP film serves as the sensing moiety. There are ~13 different capping ligands/functional groups attached to the GNPs. Upon exposure to breath samples, VOCs reach the sensing surface or diffuse into the sensing film and react with the capping ligands/functional groups, causing a volume shrinkage/expansion in the nanomaterial film [1]. As a consequence, the measured film resistance changes – increases or decreases (Figure 2: DiaNose Sensors C). Sensing responses are analysed by signal processing and artificially intelligent/pattern recognition algorithms for disease detection. (See Figure 2)

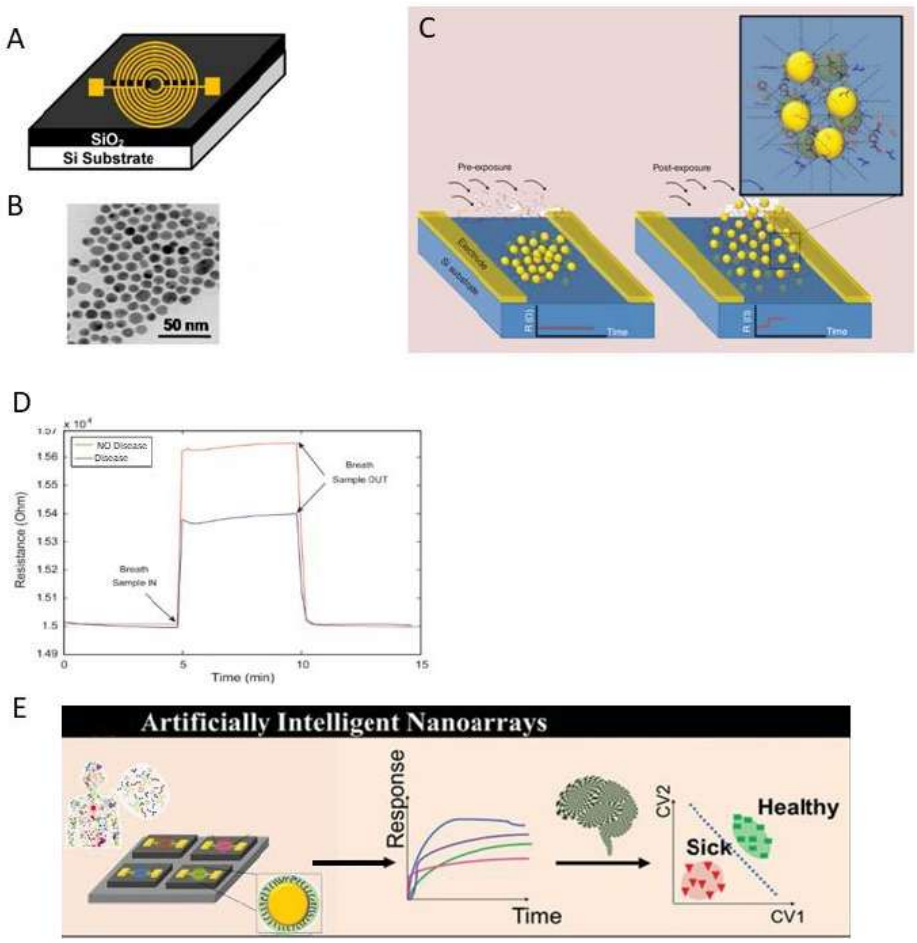


Figure 2: DiaNose Sensors - schematic representation of sensors (not drawn to scale)

a) A. Tunnelling electron micrograph image of the GNP sensing film;

b) B. General mode of operation of a typical chemiresistor based on monolayer-capped gold nanoparticles before and after exposure to VOCs;

c) C. A typical response of GNP coated sensors to the breath samples. In this example the red curve represents the measurement of a disease-free sample and the blue curve is from a positive sample.

d) D. Schematics illustrating nanomaterial-based sensors for detecting disease by means of volatile organic compounds- artificially intelligent sensing approach

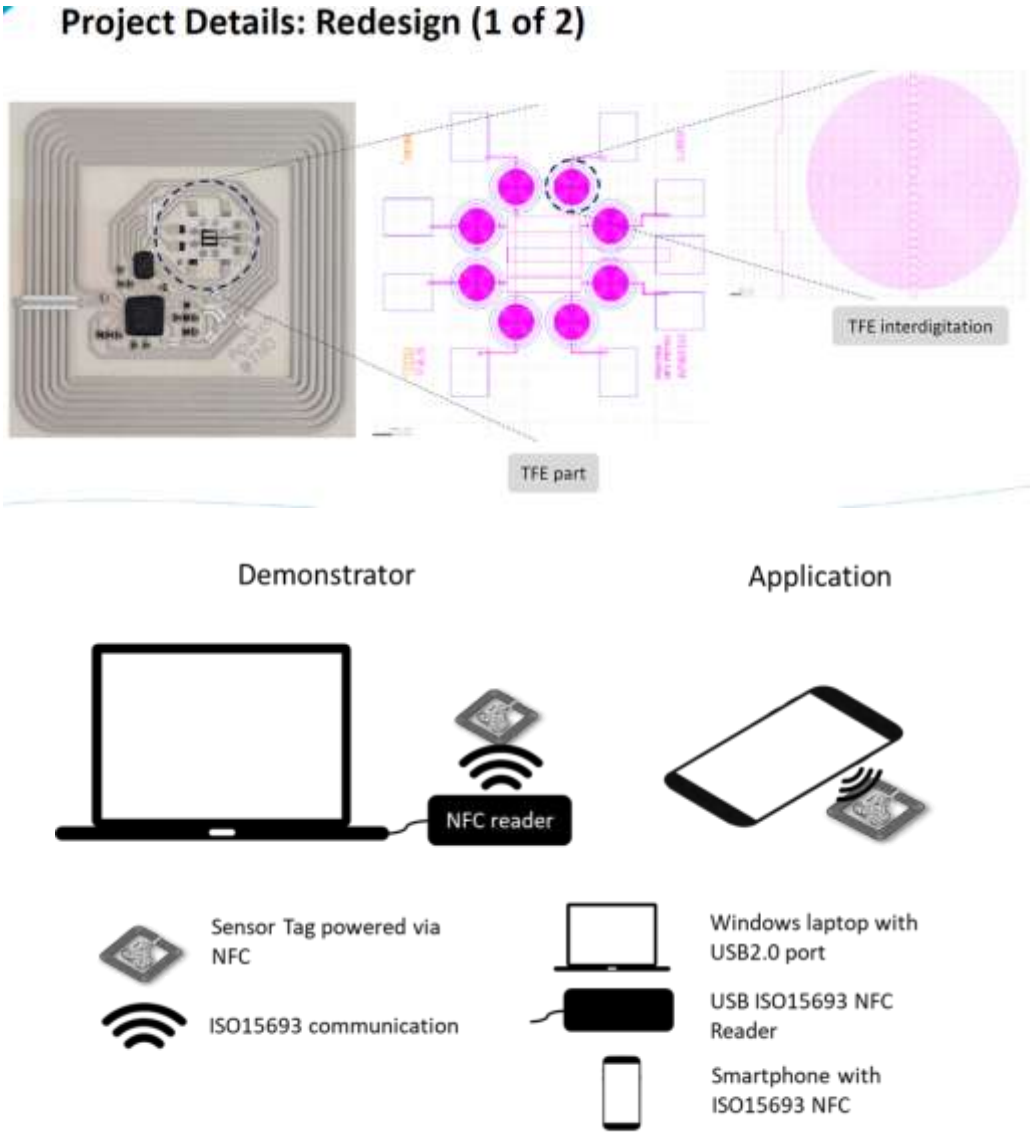
7.2 Spectrometry-on-card (SPOC): Through the use of molecule separation according to varying masses and charges, SPOC is set to identifying the volatilomic makeup from the various body fluids collected for the LC patient (e.g., blood, urine…), constitution and concentrations of VOCs, while avoiding the use of elaborate instruments or sending samples to distant labs. A sample result is ready in approximately 30 minutes. Measures VOCs of body fluid headspace (i.e., air trapped above the samples) that are linked to distinct changes in cancer biochemistry via oxidative stress, cytochrome p450, liver enzymes, carbohydrate metabolism, and/or lipid metabolism. The system pumps for 3-5 sec the headspace into the device, and as headspace pass through an array of different nanomaterial-based sensors (10 sensors), it operates according to a time-space-resolved architecture that modulate the mass-transfer rate for separation, elution and detection of each individual compound within a mixture, VOC patterns get adsorbed on the sensors, each of which emits a signal. AI and related software analyse and classify signal patterns to get a signature of LC. (See also published paper from our group on the technology concept https://doi.org/10.1002/advs.202203693)

This device is offline – a sample vial is introduced to the device with no direct contact between the volunteer and system.

7.3 Wide-biomarker-spectrum Multi-Use Sensing Patch (WBSP): the WBSP is based on the first prototype developed under the A-patch EU project (Horizon 2020 Grant Agreement Number: 824270). The latter project received ethical approval at the Technion, Israel and at the University of Latvia hospital in Riga Latvia (see attached copies of approvals). In addition, component production in TNO initially and TracXon as part of continuous development of the patch. The initial design was done at Holst Centre, as part of the a-patch work. With the fabrication of the patch in such concept, we make use of the best of both worlds: fine line patterns for the molybdenum-chromium (MoCr) sensing unit made with TFE processes and large area printing combined with component placement with HPE processes. This combination is rather new. This initial design was revised during current work at TECH together with Traxton (Holst) are shown in figure below. Patches will be put on the skin of the participants on the arm. The patch will be read (between 1 to 5 min) by a dedicated app (developed in the LUCIA project) at time zero and then after at several time points up to 1 hour (based on initial results measurement time might be extended for up to 24hour). Practically the patch itself will come in contact with the skin via only 2 components, these components are medical approved off the shelf products:

- MED 5777A, Avery Dension - An Acrylic PSA adhesive within a Thermoplastic polyethylene non-woven material. (see attached technical data sheet from manufacture).

– MED 5676A, Avery Dension - Is a single-coated, white, soft, conformable polyethylene foam with an acrylic adhesive (see attached technical data sheet from manufacture).



Patch concept has been previously assed and used. Figures Below includes the previous ethical approval as part of A-patch project (Horizon 2020 Grant Agreement Number: 824270) given in Latvia and TNO (Holst center) Netherlands.

afonds.ētika
MEDICĪNISKO UN BIOMEDICĪNISKO PĒTĪJUMU ĒTIKAS KOMITEJA

Darbojas saskaņā ar SHK LKP noteikumiem

Nr. 12-A/19
29.08.2019.
Rīgā

Rīgas Austrumu klīniskās universitātes slimnīcas atbalsta fonda
Medicīnisko un biomedicīnisko pētījumu Ētikas komitejas

ATZINUMS

Pētījuma nosaukums : *Autonoms plāksteris infekcijas slimību noteikšanai reāllaikā*

Pētījuma pieteikuma iesniedzējs: Ģirts Šķenders

Pētījuma pieteikuma iesniedzēja darba vieta: LU Klīniskās un prof. Medicīnas institūts

SIA "Rīgas Austrumu klīniskās universitātes slimnīcas" atbalsta fonda Medicīnisko un biomedicīnisko pētījumu Ētikas komiteja(sēdes prot. 08/19., 29.08.2019.) ir izvērtējusi plānotā zinātniskā pētījuma nozīmi un mērķi, iesniedzēja sniegto paredzamā ieguvuma un riska novērtējumu un tā pamatotību. Balstoties uz iesniegto dokumentu izvērtējumu, komiteja nolēma izteikt:

- ■ pozitīvu atzinumu
- ☐ negatīvu atzinumu, ar iespēju veikt izmaiņas un iesniegt pieteikumu atkārtoti
- ☐ negatīvu atzinumu

Rīgas Austrumu klīniskās universitātes slimnīcas atbalsta fonda
Medicīnisko un biomedicīnisko pētījumu
Ētikas komitejas priekšsēdētājs Roberts Stašinskis

TNO innovation for life

Memorandum

Healthy Living
Schipholweg 77-89
2316 ZL Leiden
P.O. Box 3005
2301 DA Leiden
The Netherlands

www.tno.nl

T +31 88 866 90 00

To
Charlotte Kjellander

From
TNO Institutional Review Board (IRB)

Copy to
Ton van Mol, Industry 3F

Subject
Evaluation of adhesion of health path

Date
26 October 2020

Our reference
2020-090

Contact
M.E. Hoogink-Schoevaars

Direct dialling
+31888668464

+31888665982

Background
On September 17th, 2020 the research proposal "*Evaluation of adhesion of health path*" was submitted to the TNO Institutional Review Board (IRB). The composition of the IRB is specified on the TNO Intranet page 'Human Research'.

Advice
The IRB had considered the proposed research on the basis of its regulations and expresses a positive recommendation.
The advice is determined in accordance with the methodology that can be found on the TNO Intranet page "Human Research".

In its deliberations, the IRB has considered the research design and privacy aspects, in addition to – where relevant – the ethical aspects and the burden and the risks to the research participants.
In the event of important modifications to the research or in the event incidents occur, the project leader shall inform the IRB. This may lead to amended recommendations.

Sincerely,
On behalf of the IRB,

Wilrike Pasman,
Deputy Chair Institutional Review Board TNO

Leiden, 26 October 2020
The Review Board has based its deliberations on the following submitted documents:

- Application form (11/09/2020)
- Research plan (14/09/2020)
- Participant Information Form
- Notification /Certificate of Insurance
- Quick scan DPIA

8. SECURITY

Throughout the study, an attempt will be made to minimize the risk to which the volunteers participating in it are subjected as much as possible.

The possible events that may occur during the study include the following:

The stochastic or probabilistic effects of radiation when subjected to a LDCT are difficult to determine, the literature admits an increase in the probability of having a life-threatening cancer attributable to excess radiation for a population of 60 years of age of:

- 0.09% in women and 0.05% in men for a conventional chest CT of 8mSv
- 0.011% in women and 0.006% in men for a low-dose chest CT scan of 1mSv

Regarding the security of the devices that will be used during the study:

DiaNose System: DiaNose system being developed by Nanose Medical is at investigational stage and is used to collect data of NaNose sensors response to breath samples from patients and control subjects.

During this clinical study, the system is used for data collection only. No diagnosis is performed and no medical decisions will be based on DiaNose measurements.

The method for analyzing the acceptability of an identified risk is according to the EN ISO 14971:2012 by calculating a risk index and giving acceptance indications for acceptable/ unacceptable risk.

Special considerations have been taken in designing the DiaNose system for the purpose of achieving its safe and reliable performance during the various phases of the design and development process. All preventive and/or control actions were implemented into the device so as to eliminate or reduce as much as possible any potential failure modes.

According to ISO 10993-1 DiaNose is an Externally Communicating Device, which contacts intact tissue for a Limited Contact Duration. The device is in contact with tissue (lips) for a very limited time of less than 10 seconds. The only component that comes in contact with the lips is the tube into which the tested subject exhales. We use off the shelf Polyethylene mouthpiece with wide inlet, spit trap and non-reverse valve, which is a part of measuring system of Alcotest 9510 Accessories (Draeger) for breath alcohol analysis. Many tests for approval have been performed with these mouthpieces and the device has NMI R 126:2000 approval.

Additionally, the breath collection unit into which the patient exhales that comes in contact with the lips is a disposable single use unit. The units are assembled and packed in a controlled and clean environment under laminar unit with H.E.P.A filtered air in sealed bags. Operators are trained not to use exhalation units from open bags, not to use single used unit more than once, and to discard the used unit to the biohazard trash immediately after use. The clinical app shows an alert message to throw the exhalation unit to the biohazard trash after test completion.

The DiaNose 2.5 version that is currently tested, is a passive unit connected to laptop USB (5V). DiaNose's electronic board is located inside a plastic box – there is no direct contact between users with electronic board.

Based on all the above and as detailed below, the device does not present any significant risk to the tested patient and to the operator.

Wide-biomarker-spectrum Multi-Use Sensing Patch (WBSP): the WBSP is based on the first prototype developed under the A-patch EU project (Horizon 2020 Grant Agreement Number: 824270). The latter project received ethical approval at the Technion, Israel and at the University of Latvia hospital in Riga Latvia (see attached copies of approvals). In addition, component production in TNO initially and TracXon as part of continuous development of the patch (see attached). Practically the patch itself will come in contact with the skin via only 2 components, these components are medical approved off the shelf products:

- MED 5777A, Avery Dension - An Acrylic PSA adhesive within a Thermoplastic polyethylene non-woven material. (see attached technical data sheet from manufacture).
- MED 5676A, Avery Dension - Is a single-coated, white, soft, conformable polyethylene foam with an acrylic adhesive (see attached technical data sheet from manufacture).

9. MANAGEMENT AND DATA COLLECTION

a) Data Source Identification

The source document refers to all those observations or notes recorded in the clinical interventions, as well as all the reports and notes necessary for the reconstruction and evaluation of the study Data Collection Notebook.

Basically, but not exclusively, the source documents are constituted by the documents and notes that are part of the patient's Clinical History and the different surveys that will be collected in the center.

Whenever possible, the original document should be kept as source document; however, it is acceptable to submit a photocopy as long as it is clear, legible and accurate duplicate of the original document.

The promoter shall ensure that the investigators or associated institutions allow direct access to the source data or documents for audits, for the review by the Clinical Research Ethics Committee, as well as for the inspection of the study by the health authorities (if applicable).

b) Data Quality Assurance

The Promoter will review and approve the study protocol and its possible modifications in the future, will request the authorization of the study to the Clinical Research Ethics Committee of the Basque Country, will request the agreement of the Director of the Institution, and will also be responsible for reviewing and approving the final study report.

The Principal Investigator (PI) is responsible for reviewing and approving the protocol and signing the principal investigator's commitment. The PI will ensure that the persons involved in the institution respect the confidentiality of patient information and protect personal data. The PI is also responsible for reviewing and approving the final study report together with the promoter. All members of the research team will assess the eligibility of study patients, inform and request written informed consent, collect the study source data in the medical record and transfer it to the Data Collection Notebook.

c) Data Management

The management of the collection and treatment of the study data will be carried out through the design of a Data Collection Notebook in paper format, in which the researchers assigned to this task will enter the data of each patient participating in the study.

The current legislation will be complied with in terms of data confidentiality protection (the EU General Data Protection Regulation Nr. 2016/679 (GDPR) and applicable national laws). To this end, each patient will receive an alphanumeric

identification code in the study that will not include any data allowing personal identification (coded in the Data Collection Notebook). The principal investigator will have a separate list that will allow linking the identification codes of the patients participating in the study with their clinical and personal data. This document will be filled in a secure area with restricted access, under the custody of the principal investigator and will never leave the institution.

Once the Data Collection Notebooks in paper format have been completed and closed by the principal investigator, the data will be transferred to a database.

As in the Data Collection Notebooks, the Database will comply with current legislation on data confidentiality protection (the GDPR and applicable national laws), which will not include data that allows direct identification of patients.

The transfer of data from the paper Data Collection Notebook to the electronic database will be carried out using the double data entry technique. This will be done by the researchers collaborating of the project.

Data will be managed and tabulated with consistency rules and logical ranges to control inconsistencies during data tabulation. A validation process of the clinical data will be performed by running computer filters based on validation rules, which automatically identify missing values or inconsistencies in the clinical data according to the Protocol. In addition, manual editing and validation will be performed using descriptive and exploratory statistical techniques to complement the detection of logical errors and inconsistent values.

The database shall be considered closed after the completion of all data management processes and the satisfactory resolution of discrepancies and errors in the data. Any changes to the databases after closure can only be made after written agreement between the promoter and the technical coordinators of the project.

10. ANALYSIS

Epidemiological analysis will integrate data, results and risk assessment analysis from comprehensive cross-sectional and longitudinal retrospective datasets, exposure information and multiomics-based risk analysis into risk prediction tools and evaluate their performance for both short- and long-term risk prediction in both the retrospective and prospective epidemiological and clinical cohorts included or established in LUCIA. Specific attention will

be devoted to sex- and age-specific differences and potential interactions between risk factors.

LUCIA will carry out an AI Impact Assessment (AIIA) against AI-driven risk scores and population stratification, to assess the use of AI technologies and to provide policy and ethical recommendations (incl. AI Taxonomy) moving forward. With the use of AI comes questions and concerns on the impact AI may have on individuals, society, and environment. Carried out in four steps, the AI impact assessment will address the directly affected, internal, and expert stakeholders concerned with the technologies impact on their lives, including patients, projects peers, policy makers and local stakeholders. The four steps include: (i) a materiality analysis; (ii) impact assessment; (iii) AI project (e.g., AI-based risk scores) oversight; and (iv) public / health policy recommendations. Materiality analysis will identify the most important aspects of AI projects (i.e., AI-based risk scores and AI-driven digital diagnostics) that need to be tackled to create a trustworthy AI strategy, to identify trends that could impact the project's long-term strategy, and to help in making informed decisions. Through open discussions with both the projects internal and external stakeholders, the project will be able to make use of stakeholder's insights to rank and prioritize the (critical) issues (privacy, wellbeing, safety, etc.,) most relevant to the project's strategy.

11. ETHICAL AND LEGAL CONSIDERATIONS

The development of the study will adjust to international standards of Good Clinical Practice, to the Declaration of Helsinki in its latest active amendment, and to international and national rules and regulations, and will not start until the approval of the Clinical Research Ethics Committee of the Basque Country and the agreement of the Director of the corresponding Institution. Any modification of this protocol will be reviewed and approved by the promoter and must be evaluated by the Clinical Research Ethics Committee for the approval before including subjects in a modified protocol.

The study will be carried out in accordance the GDPR and applicable national laws, which will not include any data that allows the personal identification of the subjects, and the information will be managed in encrypted form.

Patients will be informed orally and in writing about all the information related to the study and adapted to their level of understanding. A copy of the consent form and information sheet will be provided to the patient. The investigator should allow time for the patient to ask questions about the details of the trial.

The preparation of the informed consent form is the responsibility of the investigator. This form must include all the elements required by the International Conference of

Harmonization, current regulatory guidelines, and comply with the GCP Standards and ethical principles that originate from the Declaration of Helsinki.

The investigator or the Principal Investigator's designee will keep the original signed informed consent form in a secure restricted access area in the custody of the principal investigator and will never leave the site and will provide a copy of the original signed consent form to the patient.

12. PUBLICATION POLICY

All results derived from the study will be property of both the promoter and the rest of institutions involved in the study.

Promoter and researchers will commit themselves to try to have the results of this research study published in the journal with the highest possible impact, appropriate to the nature of the study and the area of knowledge to which it refers.

Any communication of the results will maintain the anonymity of the participants.

Study results or conclusions should preferably be reported in scientific publications before being released to the non-health public. Results of as yet undetermined efficacy will not be reported prematurely or sensationally, nor will they be exaggerated.

The results obtained as a consequence of the clinical investigation with the marker object under study, will be reviewed and discussed between the research team and the promoter for further publication.

When one of the parties wishes to use the partial or final results, in part or in whole, for publication in the form of an article, conference, etc., it must request the agreement of the other party or parties. The latter must respond within a maximum period of fifteen days, communicating their authorization, their reservations or their disagreement with regard to the information contained in the article or conference. If no reply is received within this period, silence shall be understood as tacit authorization for dissemination.

No information will be disseminated or presented to the public that could undermine the industrial property rights arising from the joint work. Therefore, results which, not being in themselves the subject of a patent, could disqualify, by their publication or dissemination, the recognition of the ownership of the marker or possible future product, must be considered as reserved and non-disseminated material.

13. STUDY LIMITATIONS

- Since this study involves several clinical sites across Europe with different types of populations and healthcare systems and requires a large number of patients, we may find difficulties during the recruitment to achieve the proposed sample size. This is why we will perform an interim analysis of the recruitment rate, so that we ensure a heterogeneous and complete recruitment.
- As we will recruit both healthy subjects that may develop a lung cancer and lung cancer patients for a period of 2 years, the follow up of the participants may be hindered. This could lead to a loss of patient follow up and early ending of their participation in the study.

3. Regulatory authorization reports

In this section, the Regulatory authorization reports are provided.

The 4 clinical sites (Liège, in Belgium; Riga, in Latvia; and Andalusia and the Basque Country, in Spain) submitted the clinical protocols to their respective Ethics Committees in December 2023 for its evaluation and subsequent approval. More specifically, the submission dates to the ethics committees were:

- **Andalusia**: 19/12/2023
- **Basque Country**: 22/12/2023
- **Belgium**: 06/12/2023
- **Latvia**: 15/12/2023

The regulatory authorizations of the respective regional Ethics Committees have not been obtained yet due to the thorough evaluation process that takes time. During this process, each one of the ethics committee must gather and evaluate all the documentation, before granting the approval of the study. Occasionally, these committees might require more information before approving the studies.

Therefore, until obtaining the approval of the ethics committees, we temporarily provide the request for the evaluation of research projects given by the Ethics Committees.

As soon as we obtain the approvals from the Ethics Committees, we will provide these documents for their archive and safeguard as proof of the obtaining of the regulatory authorization before the enrollment of the first participant.

In the following pages of this deliverable are shown the requests for the evaluation of research projects for the clinical sites mentioned above:

1. Andalusia Clinical Site

JUNTA DE ANDALUCIA CONSEJERÍA DE SALUD Y FAMILIAS

DOCUMENTO ESTADO DE PROYECTO

Título completo:	Understanding Lung Cancer related risk factors and their Impact Assessment
Código del estudio:	LUCIA
Promotor:	(No hay promotor/a asociado/a)
Comité:	CEI de los hospitales universitarios Vírgen Macarena-Virgen del Rocío
Protocolo:	
Versión Protocolo:	
Fecha Protocolo:	
HIP:	
Versión HIP:	
Fecha HIP:	
Solicitante:	CRISTINA SIMARRO CASTELLANOS
NIF solicitante:	06283671W
Fecha actual:	19/12/2023
Estado:	PENDIENTE DE EVALUACIÓN

Centros del proyecto

Investigador/a principal	Centros participantes	Servicio
David Vicente Baz	HOSPITAL UNIVERSITARIO VIRGEN MACARENA	
ALBERTO MORENO CONDE	HOSPITAL UNIVERSITARIO VIRGEN MACARENA	
Luis Gabriel Luque Romero	Mairena del Aljarafe Ciudad Expo	

Documentos del proyecto

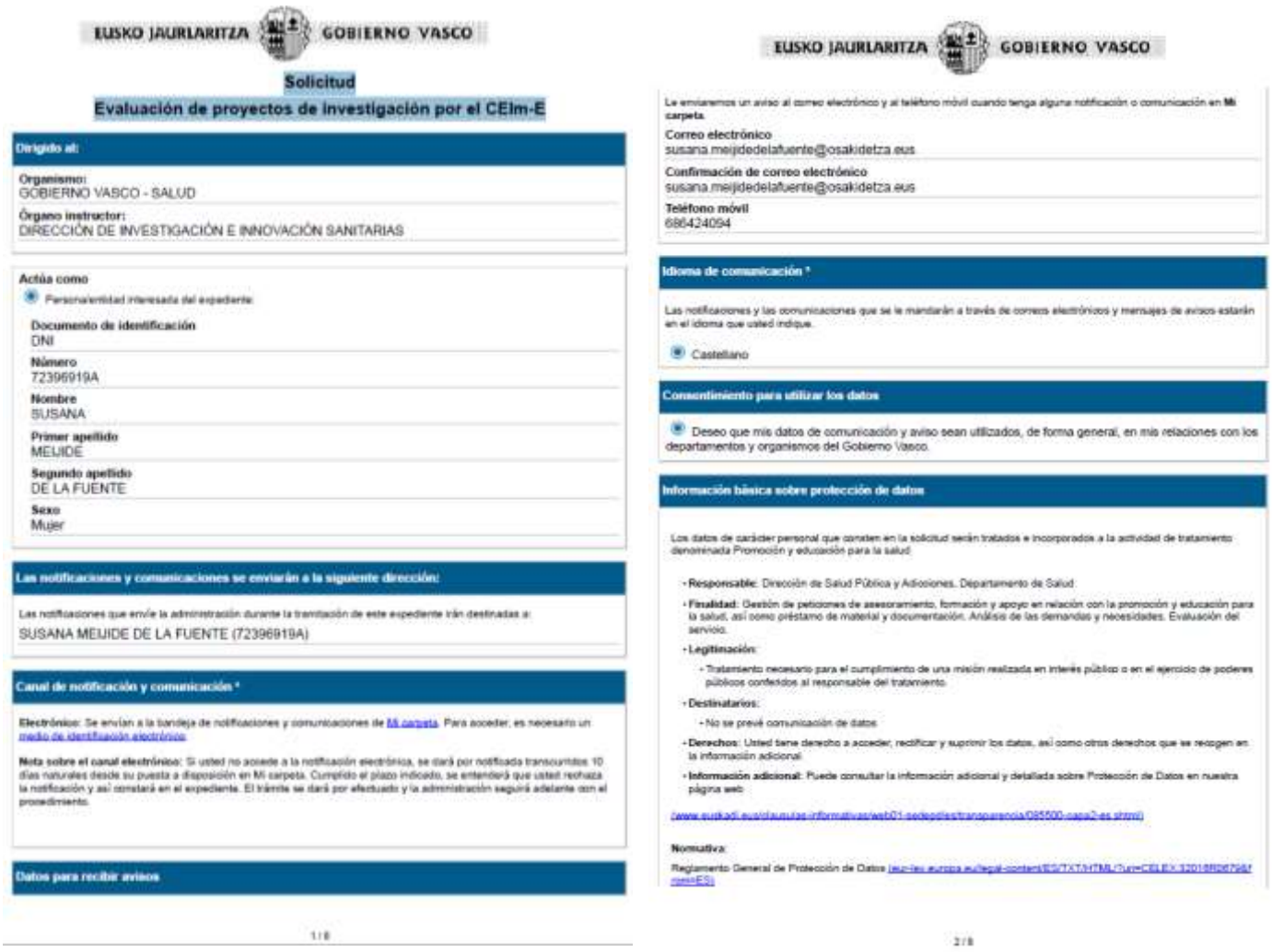
Nombre	Version	Fecha
Memoria Económica LUCIA.pdf		
cvn_COMPLETO_DVB DICIEMBRE23.pdf		
COMPROMISO INVESTIGADORES LUCIA.pdf		
HIP y CI LUCIA SAS.pdf	v.1.0	

Estados del proyecto

Estado final	Fecha
PENDIENTE DE ENVÍO	17/11/2023
ENVIADO	15/12/2023
REVISADO	18/12/2023
PENDIENTE DE EVALUACIÓN	18/12/2023

Figure 3: Request for the evaluation of research projects of the "Junta de Anadlucía" Ethics Committee

2. Basque Country Clinical Site



EUSKO JAURLARITZA GOBIERNO VASCO

Solicitud

Evaluación de proyectos de investigación por el CEIm-E

Dirigido al:

Organismo:
GOBIERNO VASCO - SALUD

Órgano instructor:
DIRECCIÓN DE INVESTIGACIÓN E INNOVACIÓN SANITARIAS

Actúa como
Persona/entidad interesada del expediente

Documento de identificación
DNI

Número
72396919A

Nombre
SUSANA

Primer apellido
MEIJIDE

Segundo apellido
DE LA FUENTE

Sexo
Mujer

Las notificaciones y comunicaciones se enviarán a la siguiente dirección:

Las notificaciones que envíe la administración durante la tramitación de este expediente irán destinadas a:
SUSANA MEIJIDE DE LA FUENTE (72396919A)

Canal de notificación y comunicación *

Electrónico: Se envían a la bandeja de notificaciones y comunicaciones de Mi carpeta. Para acceder, es necesario un medio de identificación electrónico.

Nota sobre el canal electrónico: Si usted no accede a la notificación electrónica, se dará por notificada transcurridos 10 días naturales desde su puesta a disposición en Mi carpeta. Cumplido el plazo indicado, se entenderá que usted rechaza la notificación y así constará en el expediente. El trámite se dará por efectuado y la administración seguirá adelante con el procedimiento.

Datos para recibir avisos

1 / 8

EUSKO JAURLARITZA GOBIERNO VASCO

Le enviaremos un aviso al correo electrónico y al teléfono móvil cuando tenga alguna notificación o comunicación en **Mi carpeta**.

Correo electrónico
susana.meijidedelafuente@osakidetza.eus

Confirmación de correo electrónico
susana.meijidedelafuente@osakidetza.eus

Teléfono móvil
686424094

Idioma de comunicación *

Las notificaciones y las comunicaciones que se le mandarán a través de correos electrónicos y mensajes de avisos estarán en el idioma que usted indique.

Castellano

Consentimiento para utilizar los datos

Deseo que mis datos de comunicación y aviso sean utilizados, de forma general, en mis relaciones con los departamentos y organismos del Gobierno Vasco.

Información básica sobre protección de datos

Los datos de carácter personal que consten en la solicitud serán tratados e incorporados a la actividad de tratamiento denominada Promoción y educación para la salud

- **Responsable**: Dirección de Salud Pública y Adicciones. Departamento de Salud
- **Finalidad**: Gestión de peticiones de asesoramiento, formación y apoyo en relación con la promoción y educación para la salud, así como préstamo de material y documentación. Análisis de las demandas y necesidades. Evaluación del servicio.
- **Legitimación**:
  - Tratamiento necesario para el cumplimiento de una misión realizada en interés público o en el ejercicio de poderes públicos conferidos al responsable del tratamiento.
- **Destinatarios**:
  - No se prevé comunicación de datos
- **Derechos**: Usted tiene derecho a acceder, rectificar y suprimir los datos, así como otros derechos que se recogen en la información adicional.
- **Información adicional**: Puede consultar la información adicional y detallada sobre Protección de Datos en nuestra página web

(www.euskadi.eus/privacidad-informativas/web01-sedeplec/es/transparencia/085500-capa2-es.shtml)

Normativa:

Reglamento General de Protección de Datos (eur-lex.europa.eu/legal-content/ES/TXT/HTML/?uri=CELEX:32016R0679&from=ES)

2 / 8

Figure 4: Request for the evaluation of research projects of the "Drug Research Ethics Committee" of the Basque Country

EUSKO JAURLARITZA GOBIERNO VASCO

Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales (www.boe.es/buscar/doc.php?id=BOE-A-2018-16673)

DATOS DEL ESTUDIO

Título
Understanding Lung Cancer related risk factors and their Impact

Código
LUCIA

Tipo de estudio (Clique aquí para obtener ayuda):
Proyecto de investigación biomédica / Estudio con datos

Promotor del estudio
Bs Biobizkaia

Monitor/persona de contacto
Susana Mejide de la Fuente

Versión y fecha del protocolo
versión 1.0

Escoja una opción (obligatorio clickar una):
Se solicita consentimiento informado al paciente

Versión y fecha de la Hoja de información al paciente (opción de varias HIP : 1 por línea)
Version 1.0, date 22 of DEC of 2023

Fecha prevista fin de protocolo
31/12/2027

FINANCIACIÓN

¿Se ha solicitado financiación para el estudio?
NO

¿Se realizará el estudio independientemente de la obtención de la financiación?
NO

Debe aportarse la memoria económica. Si no procede, por no conllevar pruebas o visitas extraordinarias tal y como debe reflejar en el informe del investigador*, indíquelo aquí:
NO PROCEDE

(*ver requisitos en la web: https://www.euskadi.eus/web01-a2ikerpeis/es/)

INVESTIGADORES

Número de investigadores:
8

Nota 1: Generalmente se añade un investigador por centro y servicio. No se añaden los investigadores colaboradores.

Nota 2: Si se ha clasificado el estudio como proyecto de investigación solo se incluirán los investigadores del País Vasco.

Nombre:
Iñigo

Apellidos:
Lecumberri Cortes

Servicio:
Radiología

Centro/Institución:
HU Basurto

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
si

E-mail de contacto:
INIGO.LECUMBERRICORTES@osakidetza.eus

Teléfono:
944006000

Nombre:
mikel

Apellidos:
egurrola izquierdo

Servicio:
Neumología

Centro/Institución:
Hospital de Galdakao

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
NO

E-mail de contacto:
mikel.egurrolaizquierdo@osakidetza.eus

Teléfono:
944007000

Nombre:
Irma

Apellidos:
Arrieta arbeda

Servicio:
radiología

Centro/Institución:
Hospital de Urduliz

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
NO

E-mail de contacto:
irma.arrietaarbeda@osakidetza.eus

Teléfono:
946134800

Nombre:
ESTIBALIZ

Apellidos:
PEREZ GUZMAN

Servicio:
Neumología

Centro/Institución:
hospital de San Eloy

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
NO

E-mail de contacto:
estibaliz.perezguzman@osakidetza.eus

Teléfono:
944006700

Nombre:
Larraitz

Apellidos:
garcia Echeberria

Servicio:
Neumología

Centro/Institución:
Hospital Universitario cruces

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
NO

E-mail de contacto:
larraitz.garciaecheberria@osakidetza.eus

Teléfono:
946006000

Nombre:
Iraide

Apellidos:
Exposito Herrero

Servicio:
CS mamariga

Centro/Institución:
CS mamariga

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
si

E-mail de contacto:
iraide.expositoherrero@osakidetza.eus

Teléfono:
946007680

Nombre:
Juan Miguel

Apellidos:
Campayo Perez

Servicio:
CS Baimaseda

Centro/Institución:
CS Baimaseda

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
si

E-mail de contacto:
juanmiguel.campayoperez@osakidetza.eus

Teléfono:
946102325

Nombre:
Sara

Apellidos:
De Benito Sobrado

Servicio:
CS Gordexola

Centro/Institución:
CS Gordexola

Provincia:
Bizkaia

¿Es jefe/a de servicio?:
NO

E-mail de contacto:
sara.debenitosobrado@osakidetza.eus

Teléfono:
946798023

Documentos aportados

Documentos aportados	Nombre
Aceptación de los servicios implicados	LUCIA_conformidad jefe servicio neumologia_HUB.pdf
Aceptación de los servicios implicados	LUCIA_conformidad jefe oncologia medica_HUB-1.pdf

EUSKO JAURLARITZA GOBIERNO VASCO

Documentos aportados	Nombre
Aceptación de los servicios implicados	LUCIA_conformidad jefe servicio anatomia patologica_HUC.pdf
Aceptación de los servicios implicados	LUCIA_conformidad jefe servicio neurologia_HUC.pdf
Aceptación de los servicios implicados	LUCIA_conformidad jefe servicio oncologia medica_HUC.pdf
Aceptación de los servicios implicados	LUCIA_CONFORMIDAD JEFE SERVICIO RADIODIAGNOSTICO_HUC.pdf
Aceptación de los servicios implicados	LUCIA_ conformidad jefe servicio radiologia_galdakao.pdf
Aceptación de los servicios implicados	LUCIA_conformidad jefe servicio neurologia_SANELO.pdf
Aceptación de los servicios implicados	LUCIA_CONFORMIDAD JUAP_CS_MAMARIGA.pdf
Aceptación de los servicios implicados	LUCIA_conformidad JUAP_CS_Balmaseda.pdf
Breve informe del IP en el que explique la práctica habitual en el centro	LUCIA_INFORME INVESTIGADOR_A.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_compromiso investigador neurologia_HUB_IOOR.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_compromiso IP oncologia medica_HUB-2.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_compromiso investigador neurologia_HUC.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_compromiso investigador oncologia medica_HUC.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_COMPROMISO INVESTIGADOR RADIODIAGNOSTICO_HUC.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_COMPROMISO INVESTIGADOR ANATOMIA PATOLOGICA_HUC.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_COMPROMISO INVESTIGADOR_CS_MAMARIGA.pdf
Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro)	LUCIA_compromiso investigador_CS_Balmaseda.pdf
Cuaderno de recogida de datos	LUCIA_CRD_V1.0_20122023.pdf
Documentos de consentimiento informado con versión y fecha o justificación de exención	LUCIA_HIP-CI_V1.0_20122023.pdf
Memoria científica con versión y fecha	LUCIA_Protocol_Prop_BasqueCountry_V1.0_20122023.pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_ Igor Iturbe Guallia.pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_Ainhoa Iturdiaga.pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_Eider Arkotxa.pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_LARRAITZ GARCIA.pdf

7 / 8

EUSKO JAURLARITZA GOBIERNO VASCO

Documentos aportados	Nombre
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_Marta Lázaro.pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_Isaac Esposito (corto).pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV_Monica Saiz.pdf
Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador.	CV Juan Miguel .pdf

8 / 8

Administración Pública de la CAE
Registro electrónico. Recibo de presentación de documentos

Datos del Registro

Número de registro	2023RTE015899152
Fecha de registro	22/12/23 15:49:26
Fecha de recepción de la solicitud	22/12/23 15:49:26

Interesado
72396919A - SUSANA MEIJIDE DE LA FUENTE

Destino
SALUD
DIRECCIÓN DE INVESTIGACIÓN E INNOVACIÓN SANITARIAS

Asunto
Evaluación de estudios observacionales con medicamentos, de proyectos de investigación y de productos sanitarios (CEIm-E)

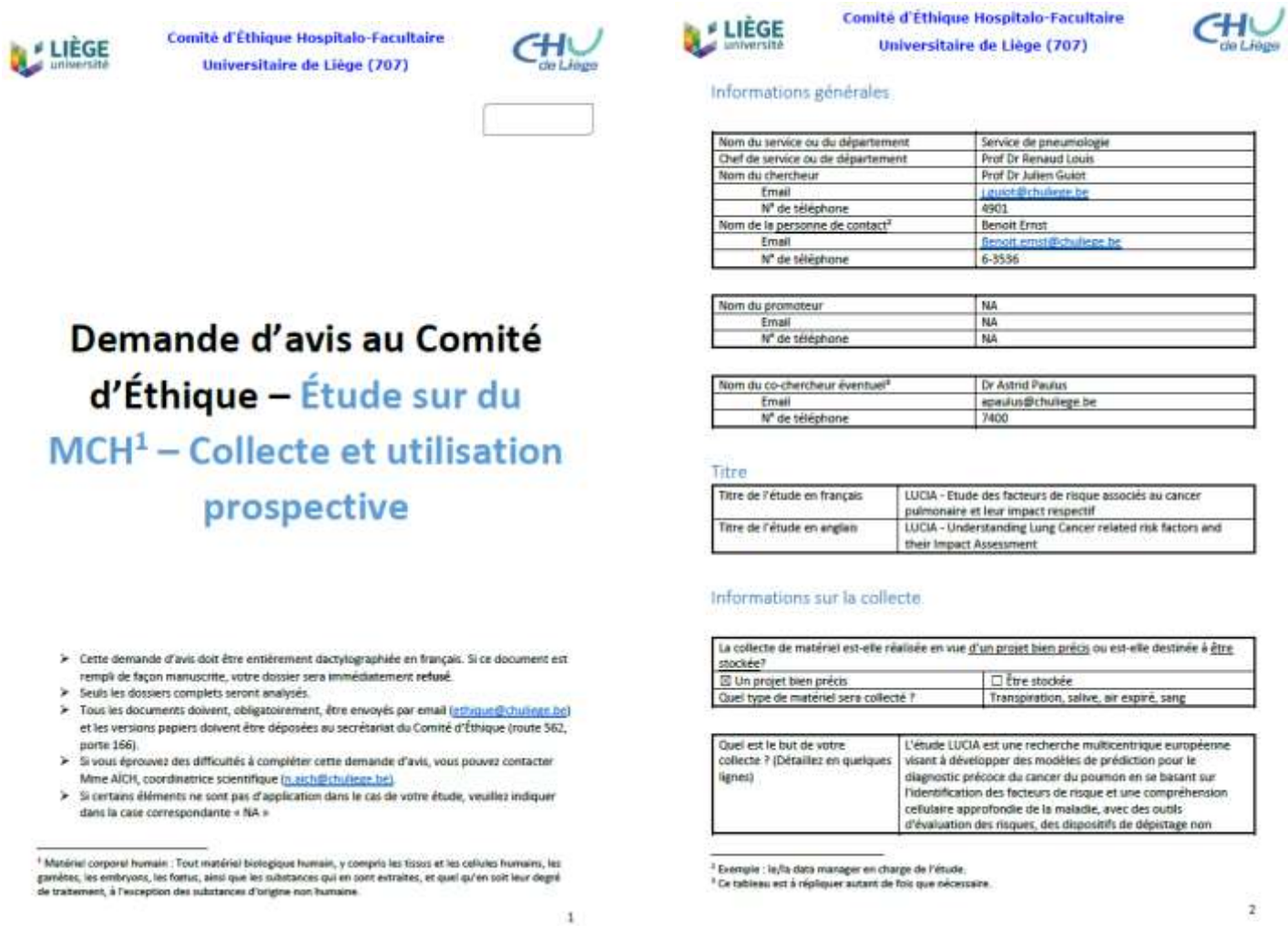
Efecto del silencio administrativo
Caducado

Plazo máximo de resolución
6 Mes(es)

Documentos anexos
» Aceptación de los servicios implicados - LUCIA_conformidad jefe servicio neuomologia_HUB.pdf
» Aceptación de los servicios implicados - LUCIA_conformidad jefe oncologia medica_HUB-1.pdf
» Aceptación de los servicios implicados - LUCIA_conformidad jefe servicio anatomia patologica_HUC.pdf
» Aceptación de los servicios implicados - LUCIA_conformidad jefe servicio neumologia_HUC.pdf
» Aceptación de los servicios implicados - LUCIA_conformidad jefe servicio oncologia medica_HUC.pdf
» Aceptación de los servicios implicados - LUCIA_CONFORMIDAD JEFE SERVICIO RADIODIAGNOSTICO_HUC.pdf
» Aceptación de los servicios implicados - LUCIA_ conformidad jefe servicio radiologia_galdakao.pdf
» Aceptación de los servicios implicados - LUCIA_conformidad jefe servicio neumologia_SANELOY.pdf
» Aceptación de los servicios implicados - LUCIA_CONFORMIDAD JUAP_CS_MAMARIGA.pdf
» Aceptación de los servicios implicados - LUCIA_conformidad JUAP_CS_Balmaseda.pdf
» Breve informe del IP en el que explique la práctica habitual en el centro - LUCIA_INFORME INVESTIGADOR_A.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_compromiso investigador neumologia_HUB_IGOR.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_compromiso IP oncologia médica_HUB-2.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_compromiso investigador neumologia_HUC.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_compromiso investigador oncologia medica_HUC.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_COMPROMISO INVESTIGADOR RADIODIAGNOSTICO_HUC.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_COMPROMISO INVESTIGADOR ANATOMIA PATOLOGICA_HUC.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_COMPROMISO INVESTIGADOR_CS_MAMARIGA.pdf
» Compromiso de todos los investigadores participantes en el País Vasco (investigador principal en cada centro) - LUCIA_compromiso investigador_CS_Balmaseda.pdf
» Cuaderno de recogida de datos - LUCIA_CRD_V1.0_22122023.pdf
» Documentos de consentimiento Informado con versión y fecha o justificación de exención - LUCIA_HIP-CI_V1.0_22122023.pdf
» Memoria científica con versión y fecha - LUCIA_Protocol_Prosp_BasqueCountry_V1.0_22122023.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_ Igor Iturbe Susilla.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_Ainhoa Gandiaga.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_Eider Azkona.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_LARRAITZ GARCIA.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_Marta Lázaro.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_Iraide Expósito (corto).pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV_Monica Saiz.pdf
» Curriculum Vitae del investigador en Euskadi, si es la primera vez que el CEIm-E evalúa un estudio de este investigador. - CV Juan Miguel .pdf
» Solicitud - Solicitud.html

» Firmado electrónicamente por:
Administración Pública de la CAE

3. Belgium Clinical Site



LIÈGE université — Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège (707) — CHU de Liège

Demande d'avis au Comité d'Éthique – Étude sur du MCH[1] – Collecte et utilisation prospective

- Cette demande d'avis doit être entièrement dactylographiée en français. Si ce document est rempli de façon manuscrite, votre dossier sera immédiatement refusé.
- Seuls les dossiers complets seront analysés.
- Tous les documents doivent, obligatoirement, être envoyés par email (ethique@chuliege.be) et les versions papiers doivent être déposées au secrétariat du Comité d'Éthique (route 562, porte 166).
- Si vous éprouvez des difficultés à compléter cette demande d'avis, vous pouvez contacter Mme AICH, coordinatrice scientifique (n.aich@chuliege.be).
- Si certains éléments ne sont pas d'application dans le cas de votre étude, veuillez indiquer dans la case correspondante « NA »

[1] Matériel corporel humain : Tout matériel biologique humain, y compris les tissus et les cellules humains, les gamètes, les embryons, les fœtus, ainsi que les substances qui en sont extraites, et quel qu'en soit leur degré de traitement, à l'exception des substances d'origine non humaine.

1

LIÈGE université — Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège (707) — CHU de Liège

Informations générales

Nom du service ou du département	Service de pneumologie
Chef de service ou de département	Prof Dr Renaud Louis
Nom du chercheur	Prof Dr Julien Guiot
Email	j.guiot@chuliege.be
N° de téléphone	4901
Nom de la personne de contact[2]	Benoit Ernst
Email	Benoit.ernst@chuliege.be
N° de téléphone	6-3536

Nom du promoteur	NA
Email	NA
N° de téléphone	NA

Nom du co-chercheur éventuel[3]	Dr Astrid Paulus
Email	apaulus@chuliege.be
N° de téléphone	7400

Titre

Titre de l'étude en français	LUCIA - Etude des facteurs de risque associés au cancer pulmonaire et leur impact respectif
Titre de l'étude en anglais	LUCIA - Understanding Lung Cancer related risk factors and their Impact Assessment

Informations sur la collecte

La collecte de matériel est-elle réalisée en vue d'un projet bien précis ou est-elle destinée à être stockée?	
☒ Un projet bien précis	☐ Être stockée
Quel type de matériel sera collecté ?	Transpiration, salive, air expiré, sang

Quel est le but de votre collecte ? (Détaillez en quelques lignes)	L'étude LUCIA est une recherche multicentrique européenne visant à développer des modèles de prédiction pour le diagnostic précoce du cancer du poumon en se basant sur l'identification des facteurs de risque et une compréhension cellulaire approfondie de la maladie, avec des outils d'évaluation des risques, des dispositifs de dépistage non

[2] Exemple : le/la data manager en charge de l'étude.
[3] Ce tableau est à répliquer autant de fois que nécessaire.

2

Figure 5: Request for the evaluation of research projects of the "Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège"

Comité d'Éthique Hospitalo-Facultaire
Universitaire de Liège (707)

	invasifs et des analyses de facteurs de risques génétiques et d'éléments retrouvés dans l'air expiré notamment.

Si vous avez un projet bien précis, quelle est la pertinence scientifique de votre projet ? (Rationale) (Détaillez en quelques lignes)	Le dépistage du cancer pulmonaire (CP) et la détection précoce peuvent avoir un impact significatif sur la réduction de la mortalité due au CP et de la mortalité globale en faisant passer une grande partie des patients d'un stade avancé, en grande partie incurable, à un stade précoce avec plus d'options de traitements curatifs, en améliorant la qualité de vie des patients et en diminuant considérablement l'impact économique sur la société. À l'heure actuelle, la méthode de dépistage du CP qui a démontré des perspectives intéressantes est le Low Dose CT Scan (LDCT). Cependant, l'utilisation du LDCT n'est recommandée que pour des populations d'âge spécifique et a suscité un débat sur ses avantages et ses inconvénients, ainsi que sur la manière dont elle peut être mise en œuvre dans une large population. Les questions en suspens les plus pertinentes sont les suivantes (i) la sous-utilisation du LDCT chez les personnes à haut risque et la surutilisation substantielle chez les personnes n'ayant pas bénéficié de dépistage et (ii) l'absence de protocoles de dépistage de CP optimisés et adaptés au risque (intervalles et durée). Pour ces raisons, l'utilisation du LDCT pour le dépistage du CP est restée très limitée, sans réduction très importante de la mortalité due au CP (20 % dans l'essai NLST et 24 % dans l'essai de dépistage NELSON). Compte tenu des coûts élevés d'un (LD)CT, de nouvelles approches sont nécessaires pour réutiliser plus efficacement les ressources du dépistage du CP grâce à une nouvelle boîte à outils qui combine une meilleure compréhension des facteurs environnementaux, génomiques et de risque du CP et des processus cellulaires liés au développement du CP. Une meilleure compréhension aurait également un impact important sur la conception de politiques de santé publique orientées vers la prévention et la détection précoce du CP, sur la base de l'expérience acquise dans le cadre de la recherche sur le CP.

Comment les donneurs seront-ils recrutés ?	Lors des consultations en pneumologie par les médecins investigateurs.
Combien de donneurs seront recrutés ?	L'objectif est 4250 inclusions tout centre confondus. Il n'y a pas d'objectif précis par centre, cela sera réévalué en cours d'étude avec un rapport intérimaire d'inclusion.
Les donneurs sont-ils des volontaires sains ?	☐ Oui ☒ Non

Comité d'Éthique Hospitalo-Facultaire
Universitaire de Liège (707)

Je m'engage à n'inclure aucun sujet avant l'obtention de l'avis favorable. Je certifie que les informations fournies, ci-dessus, sur l'étude, sont complètes et correctes et j'assume l'entière responsabilité de l'étude.	
Nom et signature du chercheur :	Prof Dr Julien Guiot
Date :	
Nom et signature du chef de service :	Prof Dr Renaud Louis
Date :	

Comité d'Éthique Hospitalo-Facultaire
Universitaire de Liège (707)

Comment avez-vous choisi la taille de votre échantillon ?	Pour atteindre une précision de 1,00 % dans l'estimation d'une proportion en utilisant un intervalle de confiance asymptotique normal bilatéral à 95,00%, en supposant que la proportion est de 8,60% (GLOBOCAN 2020 ; http://gco.iarc.fr) et un effet indésirable de 0,2 ; il a été estimé qu'il faudra inclure 4250 volontaires dans l'étude.

Dans quelle biobanque le matériel sera-t-il stocké ou tracé ?	BHUL
Qui est le gestionnaire de cette biobanque ?	Mme Stéphanie Goffiot
Nom, e-mail, téléphone :	stephanie.goffiot@chuliege.be - 4281

Étude commerciale

Est-ce une étude sponsorisée par une industrie et pour laquelle vous êtes rémunéré(e)[4] ?	☐ Oui ☒ Non

Documents nécessaires pour un dossier complet : checklist

Documents		Nb d'exemplaires	Version	Date
Demande d'avis	☒	10	V1	06/12/23
Protocole complet	☒	3	V1	06/12/23
Résumé du protocole en français (2 pages)	☒	10	V1	06/12/23
Formulaire d'information et de consentement	☒	10	V1	03/12/23
Court CV (max 3 pages) du chercheur (max 3ans)	☒	3	NA	NA
Si étude commerciale : Contrat financier	☐	1	NA	NA
Autre (Questionnaires, documents de recrutement,...)	☐	5	NA	NA

[4] Si ce n'est pas le cas, il s'agit d'une étude académique et le Comité ne demande pas de rémunération pour son évaluation.

4. Latvia Clinical Site


LINDA MEŽMALE

IESNIEGUMS
CENTRĀLĀS MEDICĪNAS ĒTIKAS KOMITEJAS ATZINUMA SAŅEMŠANAI PAR PĒTĪJUMA ATBILSTĪBU BIOĒTIKAS NORMĀM

1. Iesniedzēja nosaukums	Latvijas Universitātes Klīniskās un profilaktiskās medicīnas institūts (LU KPMI), pētnieks Linda Mežmale
2. Pētījuma nosaukums	Ar plaušu vēzi saistīto riska faktoru izpratne un to ietekmes novērtējums
3. Pētījuma mērķis	Pētījuma mērķis ir izstrādāt prognozēšanas modeļus plaušu vēža agrīnai diagnostikai, pamatojoties uz riska faktoru identificēšanu un dziļāku šūnu izpratni, izmantojot reālo datu reģistru; ar riska novērtēšanas rīkiem, neinvazīvām skrīninga ierīcēm un omikas analīzi.
4. Pētījuma zinātniskais nozīmīgums	Plaušu vēzis ir viens no izplatītākajiem audzējiem pasaulē. Piecu gadu dzīvildze dažādiem plaušu vēža veidiem svārstās no 6-7% (sīkšūnu plaušu vēzim) līdz 23–28% (nesīkšūnu plaušu vēža gadījumā). Paralēli tam strauji pieaug plaušu vēža diagnosticēšana to vidū, kas nekad nav smēķējuši. Tas savukārt liecina par to, ka ja turpināt veikt pētījumus tikai koncentrēti smēķētājiem, tiks palaisti garām citi riska faktori, kas ietekmē plaušu vēža attīstību vispārējā populācijā. Plaušu vēža skrīnings un agrīna slimības atklāšana var būtiski ietekmēt mirstības samazināšanu globāli – laicīgi atklājot slimību agrīnā stadijā ir iespējamas vairākas ārstēšanas metodes. Agrīna slimības atklāšana uzlabotu pacienta prognozi un saglabātu dzīves kvalitāti, tādejādi samazinot ekonomisko ietekmi uz sabiedrību. Šobrīd plaušu vēža skrīninga metode, kas uzrādījusi augstāku pierādījumu līmeni, ir zemas devas datortomogrāfija. Tomēr datortomogrāfijas lietošana ir ieteicama tikai noteiktām vecuma grupām, un tā ir izraisījusi plašas diskusijas par plusiem un mīnusiem, un to, kā to var ieviest liela mēroga populācijā. Būtiskākās atklātās problēmas ir šādas: nepietiekama plaušu vēža skrīninga lietošana augsta riska subjektiem un ievērojama pārmērīga lietošana cilvēkiem, kuri negūst labumu no plaušu vēža skrīninga; optimizētu, riskam pielāgotu plaušu vēža skrīninga protokolu trūkums (intervāli un ilgums) nav izveidots. Šo iemeslu dēļ datortomogrāfijas izmantošana plaušu vēža skrīningam joprojām ir ļoti ierobežota. Ņemot vērā datortomogrāfijas augstās izmaksas, ir nepieciešamas jaunas pieejas, lai efektīvāk izmantotu plaušu vēžā skrīninga resursus, izmantojot jaunu instrumentu kopumu, kas apvieno uzlabotu izpratni par plaušu vēža vides, genoma un riska faktoriem un saistītajiem šūnu procesiem plaušu vēža attīstībā. Viena stratēģija, kas varētu palīdzēt novērst šos atšķirīgos plaušu vēža skrīninga šķēršļus, ir uzlabot skrīninga efektivitāti un ieguvumus, individualizējot turpmākā plaušu vēža riska novērtējumu.

5. Iesaistītās personas	
5.1. Vadītājs/ organizators (vārds, uzvārds, telefona numurs, adrese, pielikumā Curriculum vitae)	Prof. Alvils Krams, Latvijas Universitātes Klīniskās un profilaktiskās medicīnas institūts, vadošais pētnieks, tel. +37129237807, alvils.krams@aslimnica.lv alvils.krams@gmail.com
5.2. Iesaistītie pētnieki (vārdi, uzvārdi, telefona numuri, adreses, pielikumā Curriculum vitae)	Dr. Linda Mežmale, Latvijas Universitātes Klīniskās un profilaktiskās medicīnas institūts, pētnieks, tel. +371 29918302 linda.mezmale@lu.lv Dr. med. Ilmārs Stonāns, Latvijas Universitātes Klīniskās un profilaktiskās medicīnas institūts, vadošais pētnieks, tel. +371 28655158 ilmars.stotans@lu.lc Dr. Rihards Mikilps-Mikgelbs, Latvijas Universitātes Klīniskās un profilaktiskās medicīnas institūts, zinatniskais asistents, tel. +371 29358407 rihardsmikilps@gmail.com
5.3. Iesaistītās ārstniecības iestādes vai struktūrvienības vadītāja piekrišanas pētījuma *projektam*	Rīgas Austrumu klīniskā universitātes slimnīca (RAKUS). RAKUS piekrišanas saņemšana šobrīd ir procesā un ir aizkavējusies atbildīgo darbinieku prombūtnes dēļ. Tiklīdz saņemsim apstiprinājumu, tā iesniegsim piekrišanas dokumentu CMĒK.
5.4. Kontaktpersona saziņai ar komiteju [*atzinuma nosūtīšanai*]	dr. Linda Mežmale linda.mezmale@lu.lv tel. +371 29918302

6. Informācija par pētījumu [šo sadaļu 6.-10.punkts neaizpilda, ja iesnieguma pielikumā pievienots pētījuma protokols __]	
6.1. Pētījuma veikšanas laiks (sākuma un beigu datums)	01.01.2024. – 31.12.2026. Pacientu iesaiste tiks uzsākta tikai pēc CMĒK un RAKUS atļauju iegūšanas.
6.2. Metodes	Gaistošo organisko savienojumu identificēšana, statistiskās mašīnmācīšanas algoritmi, mākslīgais intelekts, ģenētiskā testēšana, mākslīgā intelekta modeļu izveidošana, jaunu eksperimentālo ierīču izgatavošana (asins paraugu analizators – spektrometrijas karte; plaša spektra biomarķieru plāksteris biomarķieru identificēšanai sviedros, ādā), izelpas analizators, gaistošo organisko savienojumu noteikšanai.
6.3. Tehniskais aprīkojums	Spektrometrijas karte, plaša spektra biomarķieru plāksteris, izelpas analizators
6.4. Pētījuma norise	Pētījums sastāv no 3 fāzēm: 1. fāze: vispārējās populācijas skrīnings; 2. fāze: precizitātes skrīnings; 3. fāze: diagnostika. Pētījuma laikā kopumā paredzētas 4 vizītes pie pētnieka/ārsta:

Figure 6: Request for the evaluation of research projects of the "Centrālā medicīnas ētikas komiteja"

	1. sākotnēja vizīte; 2. vizīte 6 mēnesī (ieplānota attālināti); 3. vizīte 12 mēnesī; 4. vizīte 24 mēnesī. 1.fāze. Vispārējās populācijas skrīnings: identificēs iedzīvotājus ar zemu vai vidēju plaušu vēža risku, saskaņā ar izstrādāto riska faktoru novērtējumu, kas ir piemērots turpmākam skrīningam. No pētījuma subjektiem tiks ievākta informācija par sociodemogrāfiskiem datiem (vecums, dzimums, etniskā piederība, izglītības līmenis), medicīnisko vēsturi (ģimenes anamnēze, blakussaslimšanas, plašu saslimšanas), kaitīgo vielu iedarbību (alkohola lietošana, smēķēšanas status, kancerogēnu iedarbība darbā); tiks fiksēti objektīvie parametri: augums, svars, ķermeņa masas indekss, asinsspiediens, sirdsdarbība, elpošanas ātrums. Dalībniekiem būs jāaizpilda dzīves kvalitātes anketa, vidusjūras diētas ievērošanas anketa. Pētījuma dalībniekiem tiks veiktas asins analīzes, nosakot pilnu asins ainu, ĒGĀ, glikozi, CRO, kopējo olbaltumu, albumīnu, Ca, ALAT, ASAT, SF, GGT, urea, kreatinīnu, N, K. Ja pēc asins analīzes veikšanas tiks novērota novirzes no normas, pētnieks, kurš ir atbildīgs par pētījumā iesaistīto subjektu, risinās situāciju saskaņā ar parasto klīnisko praksi. Atsevišķs asins paraugs tiks nosūtīts genoma analīzei (genoma analīze tiks veikta tikai tad, ja pacients atsevišķi dos savu piekrišanu analīzei). Pētījuma dalībnieki veiks izelpu speciāli izstrādātā izelpas analizatora (izelpas biomarķieru identiciēšanai), nodos 3-5 ml asins paraugu spektometrijas kartē (biomarķieru identificēšanai). Tie subjekti, kuriem pēc izelpas testa un spektometrijas analīzes būs pozitīvi vai neskaidri rezultāti, tika novirīzi uz 2.fāzes pētījuma posmu, kur tiks veikta datortomogrāfija krūšu kurvim, kā arī tiks pielīmēts plaša spektra biomarķieru plāksteris (biomarķieru identificēšanai sviedros, ādā). Pēc 6 mēnešiem kopš 1. vizītes tiks veikta rekrutēto dalībnieku starpanalīze. Paredzēta attālināta vizīte (telefona saruna), kuras laikā tiks iegūta informācija par slimības vēsturi (jaunas diagnozes, saslimšanas epizodes, ārstēšanās stacionārā/ambulatori); kaitīgo vielu faktori (smēķēšanas uzsākšana, alkohola lietošana, kancerogēnu iedarbība darbā); tiks reģistrēti ar plaušu vēzi saistītie simptomi: klepus, kas nepāriet vai pastiprinās, asins krēpu

	atklepošana, sāpes krūtīs, kas bieži pastiprinās ar dziļu elpošanu, klepu vai smiekliem, aizdusa, apetītes zudums, neizskaidrojams svara zudums, elpas trūkums, nogurums vai vājums, infekcijas (bronhīts, pneimonija), kas nepāriet vai atkārtojas, sēkšanas epizodes. Pēc 12 mēnešiem (klātienes vizīte) kopš 1. vizītes tiks reģistrēti atkārtoti klīniskie dati, objektīvā atradne. Tiks reģistrēti ar plaušu vēzi saistītie simptomi. Pēc 24 mēnešiem (klātienes vizīte) kopš 1. vizītes tiks reģistrēti atkārtoti klīniskie dati, objektīvā atradne. Pētījuma dalībniekiem tiks veiks izelpu tests speciāli izstrādātā izelpas analizātorā (izelpas biomarķieru identiciēšanai), atkārtoti būs nepieciešams nodot 3-5 ml asins paraugu spektometrijas kartē (biomarķieru identificēšanai). 2.fāze. Precizitātes skrīnings: identificēs iedzīvotājus ar paaugstinātu risku saslimt ar plaušu vēzi saskaņā ar izstrādāto riska faktoru novērtējumu, kas ir piemērots turpmākam skrīningam, izmantojot zemu izmaksu ierīces kopienas apstākļos vai centralizētās skrīninga iestādēs. 3. fāze Diagnoze: riska faktoru novērtēšanas rīka ievades izmantošana kopā ar biomarķieriem palīdzēs diferencēt diagnozes darbplūsmu, paātrināt diagnostikas procedūru un uzsākt vispiemērotāko ārstēšanas režīmu. Šajā fāzē tiks iekļauti tie dalībnieki, kam skrīninga fāzē tika diagnosticēts plašu vēzis vai nenoteikti plašu mezgliņi. Ja būs nepieciešams sasniegt nepieciešami pacietnu skaitu, papildus tam tiks rekrtutēti sekojoši pacienti: - pacienti ar jaunu plaušu mezgliņu vai plaušu vēža diagnozi, pirms ārstēšanas uzsākšanas ārpus skrīninga fāzēm no pneimologa konsultācijām; - CT skrīninga pacienti, kuri nosūtīti uz turpmāku skenēšanu nenoteiktu plaušu mezglu klātbūtnes dēļ; - pacienti ar diagnosticētu plašu vēzi (no stacionāra vai pneimonologa konsultācijām). 3. fāzes dalībniekiem tiks veiktas analoģiskas asins analīzes kā pie fāzes 1., veikts izelpas tests; būs nepieciešams nodot 3-5 ml asins paraugu spektometrijas kartē; pielīmēts plaša spektra biomarķieru plāksteris (biomarķieru identificēšanai sviedros, ādā).

6.5. Dalībnieku skaits, raksturojums, iekļaušanas un izslēgšanas kritēriji	1000 dalībnieki Iekļaušanas kritēriji: – abu dzimumu subjekti vecumā no 40 līdz 80 gadiem, kuri vēlas un spēs ievērot pētījuma protokolu veiks visus nepieciešamos laboratorijas testus un izmeklējumus, kas būs nepieciešami pētījuma ietvaros, pirms tam parakstot informētās piekrišanas formu. Izslēgšanas kritēriji: – subjekti jaunāki par 40 gadiem; – subjekti, kuriem nevarēs veikt uzraudzību vismaz 2 gadus, vai tie, kas nevarēs piedalīties pētījumā līdz galam; – subjekti, kuri neparaksta informētās piekrišanas formu; – šobrīd vai iepriekš bijis plaušu vēzis; – pēdējo piecu gadu laikā bija diagnosticēts cits ļaundabīgs audzējs, izņemot nemelanomas ādas vēzi; – vidēji smagas vai smagas blakusslimības, kas neļauj pabeigt pētījumu, ja tiek konstatēti atradumi, kas liecina par plaušu jaunveidojumu (pēc pētnieka klīniskā sprieduma) vai ķirurģiskās iejaukšanās (<6 mēneši), ja iepriekš nav apstiprināts ar citohistoloģisko izmeklēšanu; – neaizsargātas personas: subjekti ar smagām psihiskām slimībām; aizbildnībā esošās personas; personas, kuriem atņemta brīvība; – grūtnieces.

7. Pētījuma dalībnieki ar īpašām vajadzībām	JĀ	NĒ
7.1. Nepilngadīgie		X
7.2. Neatliekamās medicīniskās palīdzības pacienti		X
7.3. Personas, kuras nav spējīgas paust savu gribu		X
7.4. Ieslodzītie		X
7.5. Grūtnieces		X
7.6. Mātes, kas zīda bērnus		X
7.7. Cita aizsargājama grupa: _____		X
8. Informētās piekrišanas veids		
8.1. Vai pētījuma dalībnieki parakstīs informētās piekrišanas veidlapu?	X	
8.2. Vai pētījuma dalībnieku likumiskie pārstāvji parakstīs informētās piekrišanas veidlapu?		X
8.3. Vai pētījuma dalībnieki sniegs informēto piekrišanu dalībai pētījumā citā veidā, neparakstot informētās piekrišanas veidlapu (*piemēram, anonīmā aptaujā*)?		X

8.4. Kas, kad un kādā veidā veiks informētās piekrišanas procedūru, t.sk. kā tiks informēti nepilngadīgie pētījuma dalībnieki un personas, kuras nav spējīgas paust savu gribu?	Pētnieki potenciāliem pētījuma dalībniekiem izskaidros pētījuma mērķi, gaitu, paredzētās aktivitātes pētījuma ietvaros. Papildus tam tiks izsniegta arī rakstiska informācija par pētījuma norisi, informētās piekrišanas forma. Potenciāls pētījuma dalībnieks tiks iekļauts pētījumā tikai tad, kad iepazīsies ar izsniegtiem dokumentiem, parakstīs informētās piekrišanas formu.
9. Izmantotie bioloģiskie paraugi	
9.1. Vai pētījumā tiks iegūti un/vai izmantoti cilvēka izcelsmes bioloģiskie paraugi? Ja jā, detalizēti aprakstiet plānoto paraugu skaitu, veidus, ieguves procesu.	No pacientiem tiek iegūti asins paraugi (standarta analīzes noteikšanai; genoma analīzei; spektrometrijas analīzei, nosakot gaistošos biomerķierus asinīs), izelpas paraugi (gaistošo biomarķieru noteikšanai), sviedri (tiks iegūti no plaša spektra biomarķieru plākstera, biomarķieru identificēšanai).
9.2. Vai pētījumā tiks izmantotas cilvēka *šūnu līnijas*? Ja jā, detalizēti aprakstiet šūnu līniju veidu un ieguves avotu.	Nav paredzēts.
9.3. Cik ilgi un kā tiks uzglabāti pētījumā izmantotie cilvēka izcelsmes bioloģiskie paraugi?	Pēc paraugu analizēšanas un rezultātu ievadīšanas datubāzē, bioloģiskie paraugi tiks utilizēti atbilstoši laboratorijas iekšējām standarta procedūrām.
9.4. Kas notiks ar pētījuma ietvaros iegūtajiem bioloģiskajiem paraugiem, ja persona pārtrauks dalību pētījumā?	Pētījumā izmantotie bioloģiskie paraugi tiks utilizēti atbilstoši laboratorijas iekšējām standarta procedūrām.
10. Risku un ieguvumu analīze	
10.1. Kādi ir fiziskie un/vai psiholoģiskie riski pētījuma dalībniekiem?	Iespējams diskomforts, kas rodas noņemot adhezīvus neliela izmēra plāksterus. Asins parauga ņemšanas vietā retos gadījumos var rasties neliels asins izplūdums, vai vēl retāk - neliels lokāls ādas iekaisums. Ir iespējami sarežģījumi saistībā ar CT veikšanu, tomēr tie tiks atrunāti pacienta informētās piekrišanas formās, kas tiek izmantotas medicīnas iestādēs konkrētajai manipulācijai.
10.2. Kādi pasākumi tiks veikti risku samazināšanai un pētījuma dalībnieku aizsardzībai?	Pētījuma dalībnieki saņems detalizētu informāciju par katru pētījuma posmu, veiktajām manipulācijām.
10.3. Kāds ir pētījuma rezultātā *sagaidāmais ieguvums sabiedrībai*?	Pētījuma laikā tiks izstrādātas potenciāli jaunas plaušu vēžā skrīninga metodes; izstrādātie prognozēšanas modeļi plaušu vēža agrīnai diagnostikai sniegs jaunas zināšanas par plaušu vēža attīstību, riska faktoriem.
10.4. Kāds ir pētījuma rezultātā sagaidāmais ieguvums pētījuma dalībniekiem (ja šāds ieguvums ir sagaidāms)?	Dalībai šajā pētījumā nebūs tiešas ietekmes uz pacienta veselības stāvokli un ārstēšanu, subjektu ziedotie bioloģiskie paraugi un sniegtās atbildes uz jautājumiem var palīdzēt izstrādāt metodes, ar kurām ātrāk un precīzāk diagnosticētu plaušu vēzi. Turklāt dalība šajā pētījumā veicinās ilgtermiņa saslimstības un

	mirstības samazināšanos no plaušu vēža, un laus nākotnē īstenot plaušu vēža skrīningu.
10.5. Vai pētījumā pastāv iespēja iegūt nozīmīgu informāciju par pētījuma dalībnieku veselību (individuāli pētījuma rezultāti, sekundāri pētījuma rezultāti, negaidīti atradumi)? Ja jā, aprakstiet rīcības plānu šādiem gadījumiem - vai un kā par šādu informāciju tiks informēti pētījuma dalībnieki?	Ja tiks noteikta nozīmīga informācija par pētījuma subjektu veselības stāvokli, tad atbildīgais pētnieks risinās situāciju saskaņā ar standarta klīnisko praksi kopā ar ārstējošo ārstu (subjektu nosūtīs pie konktrēta specialista, pēc nepieciešamības ārstējošais ārsts nosūtīs papildus izmeklējumu veikšanai).
10.6. Vai pētījuma rezultāti var radīt diskriminācijas vai stigmatizācijas riskus pētījuma dalībniekiem vai viņu pārstāvētājām sabiedrības grupām? Ja jā, aprakstiet šos riskus un pasākumus risku samazināšanai.	Pētījuma rezultāti nevar rādīt diskriminācijas vai stigmatizācijas riskus pētījuma dalībniekiem vai viņu pārstāvētājām sabiedrības grupām.

11. Ētiskie apsvērumi	
11.1. Apliecinājums, ka pētījums tiks veikts saskaņā ar *Pasaules Medicīnas asociācijas Taipejas deklarāciju, Pasaules Medicīnas asociācijas Helsinku deklarāciju, Konvencija par cilvēktiesību un cieņas aizsardzību bioloģijā un medicīnā - Konvencija par cilvēktiesībām un biomedicīnu* [Ovjedo konvenciju] un normatīvajiem aktiem	Pētījums tiks veikts saskaņā ar Pasaules Medicīnas asociācijas Helsinku deklarāciju un Eiropas Padomes Konvenciju par cilvēktiesību un cilvēka cieņas aizsardzību bioloģijā un medicīnā un sekojošiem Latvijas Republikā spēkā esošiem likumiem un normatīviem aktiem: • Cilvēka genoma izpētes likums. 13.06.2002; • Fizisko personu datu apstrādes likums 21.06.2018. • Pacientu tiesību likums. 17.12.2009.
11.2. Apliecinājums, ka pētījumā, izmantojot autopsijas materiālu, tiks ievērotas likumu "*Par miruša cilvēka ķermeņa aizsardzību un cilvēka audu un orgānu izmantošanu medicīnā*" prasības	Nav paredzēts izmantot autopsijas materiālu pētījumā.
11.3. Apliecinājums, ka bērni pētījumā tiks iekļauti tikai pēc tam, kad būs saņemts bērna likumiskā vai ieceltā pārstāvja rakstisks apliecinājums par pētījuma skaidrojuma saņemšanu un piekrišanu dalībai pētījumā. Bērna tiesības tiks respektētas atbilstoši spēkā esošajiem normatīvajiem aktiem.	Nav paredzēts iekļaut bērnus pētījumā.
11.4. Apliecinājums, ka pētījumā lēmumu pieņemt nespējīgi pieauguši pētījuma dalībnieki tiks iekļauti tikai pēc rakstiskas piekrišanas saņemšanas atbilstoši Pacientu tiesību likuma 7.pantam, ja pētījums ir indicēts atbilstoši medicīnas zinātnes atziņām	Nav paredzēts iekļaut pieaugušos, kas nespējīgi pieņemt lēmumu par dalību pētījumā.
11.5. Apliecinājums, ka pētījuma veikšanai ņemtais bioloģiskais materiāls tiks izmantots tikai konkrētā pētījuma mērķim	LU KPMI iesaistītie pētnieki apliecina, ka ņemtie bioloģiskie paraugi tiks izmantoti tikai konkrētā pētījuma mērķim.
11.6. Apliecinājums par kompensāciju pētījuma dalībniekam sarežģījumu gadījumos	Veselības sarežģījumu riski šajā projektā nav paredzami. Kompensācija par kaitējumu pētījuma dalībnieku privātumam, ja sensitīvie dati vai izpētes rezultāti tikuši nelikumīgi nodoti trešajai personai, tiek piedzīta Latvijas likumdošanā paredzētajā kārtībā, izskatot šādus gadījumus individuāli.
11.7. Apliecinājumu, ka pētījuma priekšlaicīgas pārtraukšanas gadījumā, rakstisks ziņojums par iemesliem, tiks nekavējoties nosūtīts Centrālai medicīnas ētikas komitejai	LU KPMI iesaistītie pētnieki apliecina, ka pētījuma priekšlaicīgas pārtraukšanas gadījumā, tiks sniegts rakstisks ziņojums par pētījuma pārtraukšanas iemesliem Centrālai medicīnas ētikas komitejai.
11.8. Apliecinājumu, ka izmaiņas protokolā tiks iesniegtas komitejai apstiprināšanai (atzinuma sniegšanai)	LU KPMI iesaistītie pētnieki apliecina, ka gadījumā, ja tiks veiktas izmaiņas pētījuma protokolā, tad izmaiņas tiks atkārtoti iesniegtas Centrālās medicīnas ētikas komitejai.

12. Personas datu apstrāde [šo punktu neaizpilda, ja iesnieguma pielikumā pievienots Datu aizsardzības speciālista apliecinājumu par] *(Būtiski pseidonimizēti dati arī ir personas dati!)*	
12.1. Vai pētījuma ietvaros tiks iegūti un apstrādāti īpašo kategoriju personas dati (ģenētiskie dati, biometriskie dati, dati, kas atklāj rases, etnisko piederību, politiskos uzskatus, reliģisko, filozofisko pārliecību, dalību arodbiedrībās, veselības dati, dati par personas dzimumdzīvi vai seksuālo orientāciju)? Ja jā, detalizēti aprakstiet personas datu veidu un avotu.	No pētījuma dalībniekiem tiks ievākti dati par sekojošu informāciju: ○ Vecums, dzimums, etniskā piederība, sociālekonomiskie faktori, deprivācijas indekss, izglītības līmenis un fiziskās apskates dati. ○ Medicīniskā vēsture un kaitīgo vielu iedarbība. ○ Dati no anketām par dzīves kvalitāti (pacients pildīs patstāvīgi). ○ Dati par datortomogrāfijas izmeklējumu (apraksts). Pētījuma dalībniekiem personīgi tiks uzdoti jautājumi par iepriekšminētie punktiem. Pēc nepieciešamības, pētījuma dalībniekiem tiks palūgts sniegt nepieciešamos dokumentus, kas apstiprina konkrētas diagnozes, izmeklējumu aprakstus.
12.2. Vai pētījuma ietvaros tiks veikta personas datu pseidonimizācija vai anonimizācija? Ja jā, aprakstiet pseidonimizācijas un/vai anonimizācijas procesus.	Personas dati tiks uzglabāti kodētā veidā, katram pacientam piešķirot unikālu identifikācijas kodu. Kodētā informācija un ar to saistītais identifikācijas saraksts (kodu atslēgas) glabāsies atsevišķi. Kodu atslēgas iespējams identificēt tikai klīniskā centra ietvaros noteiktam darbinieku lokam ar lietotāja vārdu un piekļuves parolēm (atslēgām). Personas datiem būs ierobežots pieejamības statuss – informācija paredzēta tikai noteiktam darbinieku lokam ar lietotāja vārdu un

	piekļuves parolēm (atslēgām), un datu apstrādi veic tikai pilnvaroti darbinieki.
12.3. Cik ilgi, kur un kā tiks uzglabāti personas dati?	Pēc pētījuma beigām personas dati tiks glabāti projekta datubāzē 10 gadus, pamatojoties uz sekojošām saistībām: • ES tiesību akti, piemēram, personas dati, kas potenciāli ietverti dokumentācijā, uz kuru attiecas Regulas (ES) 2017/745 par medicīnas ierīcēm XV pielikuma III nodaļa. • Turklāt dati ir jāuzglabā 5 gadus pēc pētījuma beigām kā daļa no projekta konsorcija saistībām pret Eiropas Komisiju saskaņā ar programmu "Apvārsnis Eiropa". Pēc 10 gadu perioda ar personu saistītie dati tiks dzēsti, ja vien nepastāvēs citi juridiski pienākumi, kas liks datus uzglabāt vēl ilgāku laiku. Personas dati tiks uzglabāti kodētā veidā, katram pacientam piešķirot unikālu identifikācijas kodu. Kodētā informācija un ar to saistītais identifikācijas saraksts (kodu atslēgas) glabāsies atsevišķi.
12.4. Kam būs piekļuve personas datiem pētījuma ietvaros?	Personas datiem būs ierobežots pieejamības statuss – informācija paredzēta tikai noteiktam darbinieku lokam ar lietotāja vārdu un piekļuves parolēm (atslēgām), un datu apstrādi veiks tikai pilnvaroti darbinieki.
12.5. Kas notiks ar personas datiem, ja persona pārtrauks dalību pētījumā?	Subjekta personas dati tiks dzēsti no pētījuma datubāzes.
12.6. Vai pētījumā notiks sekundāra iepriekš citiem mērķiem iegūtu personas datu apstrāde (piemēram, no pētījuma dalībnieku medicīniskajiem dokumentiem, reģistriem, datu bāzēm, arhīviem)? Ja jā, kāds būs datu avots un likumiskais pamats datu apstrādei?	Nav paredzēts.
12.7. Vai pētījumā ir plānota pētījuma dalībnieku novērošana vai izsekošana (piemēram, ievācot ģeolokācijas datus ar elektronisku ierīču palīdzību)?	Paredzēts noteikt dzīvesvietas ģeolokāciju, pamatojoties uz pētījuma dalībnieku sniegto atbildi. Ģeolokācijas noteikšana nepieciešama, lai identificētu potenciālos plauša vēžā ārējos riska faktorus (piemēram, rūpnīcas, fabrikas u.c.).
12.8. Vai pētījuma dalībniekiem tiks sniegta personas datu pārziņa kontaktinformācija?	Jā, tā ir norādīta informētā piekrišanā.

13. Starptautiskā sadarbība	
13.1. Vai pētījumā ir iesaistīti sadarbības partneri ārpus ES valstīm? Ja jā, miniet valstis.	Technion (Izraela): pētījuma laikā analizēs gaistošo organisko savienojumu paraugus (izelpas iekārtām un spektrometrijas kartēm), pamatojoties uz pseidonimizētiem personas datiem, veidos mašīnmācīšanās klasifikatora algoritmu. Emoda Yazilim Ve Danismanlik Sanayi Ticaret Limited Sirketi (Turcija): apkopos datus eksperimentālām ierīcēm, atbalstīs datu ievadi un vizualizāciju, kā arī veidos mākslīgā intelekta riska faktoru modeļus, pamatojoties uz pseidonimizētiem datiem. University of Ulster (Apvienotā Karaliste): veiks vides un sociāldemogrāfisko datu riska faktoru analīzi, izmantojot ģeotelpisko analīzi un mašīnmācīšanās metodes, un izstrādās mākslīgā intelekta modeļus, pamatojoties uz dalībnieku pseidonimizētiem datiem.
13.2. Vai pētījuma ietvaros ir plānots importēt/eksportēt personas datus no/uz ES valstīm vai valstīm ārpus ES? Ja jā, detalizēti aprakstiet plānotās darbības.	Personas dati tiks importēti no/uz ES valstīm un uz valstīm ārpus ES. Personas dati būs pseidonimizēti, tādēļ konkrētas personas nevarēs identificēt. Pseidomizētu datu apmaiņa notiks caur projekta laikā izstrādāto datu bāzi.
13.3. Vai pētījuma ietvaros ir plānots importēt/eksportēt cilvēka izcelsmes bioloģiskos paraugus vai šūnu līnijas no/uz ES valstīm vai valstīm ārpus ES? Ja jā, detalizēti aprakstiet plānotās darbības.	Asins paraugi genoma analīzei tiks apstrādāti un analizēti ES, Spānijā, "Centro Nacional de Análisis Genómico" (CNAG, www.cnag.eu). Paredzēts veikt visa genoma sekvencēšanu, lai identificētu epigenomiskās izmaiņas visos gēnos un starpgēnu reģionos. No šiem paraugiem iegūtie dati tiks glabāti un apstrādāti CNAG datu centrā, kas paredzēts liela datu apjoma apstrādei, uzglabāšanai un pārvaldībai. Šīm datu centram var piekļūt tikai CNAG pilnvarots personāls saskaņā ar stingrajiem ISO 27001 (informācijas drošības, kiberdrošības un privātuma aizsardzības pārvaldības sistēmas) nosacījumiem, ko pārrauga datu aizsardzības speciālists (dpo@cnag.eu). CNAG procesi atbilst ISO 9001 kvalitātes vadības sistēmu sertifikācijai un ir akreditēti ar ISO 17025, nodrošinot kompetenci un derīgu rezultātu ģenerēšanu.
13.4. Citas valsts bioētikas komitejas atzinums (ja tāds jau ir) par multilaterāla pētījuma veikšanu	Pētījuma klīniskā norise tiek realizēta Latvijā un Eiropas klīniskajos centros (Beļģijā – "Centre Hospitalier Universitaire de Liège", Spānijā – "Servicio Andaluz de Salud Servicio", "Vasco de Salud Osakidetza" un "Biocruces Bizkaia Health Research Institute"). Šobrīd visi iesaistītie klīniskie centri iesnieguši pētījumu protokolus ētikas atzīšanai savās valstīs.

14. Finansējuma avots (pasūtītājs)	Horizon 2021, projekta numurs: 101096473

15. Pielikumā	**Pievienotās datnes nosaukums**
15.1. Informācija pētījuma dalībniekam par pētījumu un informētā piekrišana dalībai pētījumā un datu apstrādei	

Datums 15.12.2023. Paraksts

4. Annexes

1. General population Screening Clinical Protocols:

In this section, we include the screenshots of the "*Clinical Management and Study Plans*" sections of each one of the Clinical Sites (Andalusia, Basque Country, Belgium and Latvia) for the General Population Screening:

a. Andalusia clinical site

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7. CLINICAL MANAGEMENT AND STUDY PLAN

PHASE 1 study: General population screening: *Identify citizens with low to moderate risk of LC according to the developed risk factor assessment tools, suitable for further screening using low-cost devices in community-based settings or in centralized screening facilities.*

VISIT 1 - Baseline

Clinicians from the different clinical centers will identify possible participants from their consultations. These participants will be both smokers and never smokers & reduced smokers with low to moderate risk of Lung Cancer who meet the criteria generated by risk factor assessment tools.

Recruitment will ensure only eligible participants are included so that relevant and high-quality data is collected. Targets will be set to ensure research activities are delivered on time. All possible measures will be taken to ensure there is no discrimination or harms from the recruitment, exclusion or inclusion process.

On the first day of visit 1 or baseline, the principal investigators and their team of collaborators will review the eligibility of patients who meet the inclusion criteria and none of the exclusion criteria, established in sections 4.4.1 and 4.4.2.

Recruitment will be carried out by the main investigator and/or the co-investigators authorized to do so at the General Practitioner and/or pneumologist's consultation. The researcher will proceed to inform the selected patients about the possibility of participating in the clinical trial by explaining them what their participation will consist of through the Patient Information Sheet and the Informed Consent. The participants will be able to ask all the questions they deem appropriate in order to clarify all their doubts and will take the time they consider necessary to decide.

If the patient wishes to participate in the study, they will sign the Informed Consent and a code will be assigned to guaranty the pseudoanonymization of the patient and included in the participant's electronic health record (EHR).

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The code will be as it goes:

LUCIA-XX-####

Being:

XX: the code of the site where the patient has been recruited (AN for Andalusia, BC for Basque Country, LI for Liège and RI for Riga)

####: the number of patient recruited (consecutive numbers in order of recruitment from 0001 to 1,000)

During this first visit, the principal investigator and/or their collaborators will access the EHR of each patient and will record the clinical data:

Sociodemographic data: Age, Gender, Ethnicity, socioeconomic factors, deprivation index, education level.

Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.

Spirometry result.

Medical record: Family history of lung cancer or other types of cancer, emphysema/ COPD/ asthma, Interstitial Lung Disease (interstitial patterns), bronchiectasis, arterial hypertension, dyslipidemia, previous acute myocardial infarction, vasculopathies and chronic treatment.

Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

Lifestyle Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence test and EuroQoL.

Geo-location

Investigators will collect a blood sample of the participants for its analysis, including:

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General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Cholesterol, transferrin, phosphate, calcium

Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase

Kidney profile: urea, Creatinine, Sodium, potassium, Urate

General haematology: blood count, erythrocyte sedimentation rate

Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time

Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

If abnormal values are observed after performing the blood analysis, the researcher in charge of the subject involved in the study will handle the situation according to usual clinical practice.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification

Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

All these data will be entered in the Case Report Form (CRF) of the study developed by Bilbomática.

Based on the devices (individuals who show positive or uncertain results) and by AI analysis risk factor model, subjects will:

Continue in **Phase 1: Wide population Screening** if low-moderate risk of lung cancer is assigned by AI analysis.

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Be referred to **Phase 2: Precision Screening** and included within polygenetic scoring analysis if high risk of lung cancer is assigned by validated Lung Cancer risk factors AI model.

Be referred to **Phase 3: Diagnosis** if by results of LDCT lung cancer or Indeterminate Pulmonary Nodules (IPN) are found.

Follow up visit 2 (6 months ± 30 days)

6 months after the beginning of the project an interim analysis of the recruited patients will be carried out to verify the heterogeneity of the sample and to ensure that we comply with the representativeness of each group in the study.

If the minimum percentage of subject per group is not achieved, the recruitment will follow in the misrepresented group until the balance is restored.

This visit will be performed remotely.

During this visit, the following information will be recorded:

Medical record: New diagnoses, clinical episodes and/or treatments.

Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

Guide symptoms of a possible Lung Cancer will also be recorded:

A cough that does not go away or gets worse

Coughing up blood or rust-colored sputum (spit or phlegm)

Chest pain that is often worse with deep breathing, coughing, or laughing

Hoarseness

Loss of appetite

Unexplained weight loss

Shortness of breath

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Feeling tired or weak

Infections such as bronchitis and pneumonia that don't go away or keep coming back

New onset of wheezing

Follow up visit 3 (12 months ± 2 months)

During the follow up visits (12 months from visit 1), clinical data and questionnaires will be recorded:

Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate

Spirometry result.

Medical record: New diagnoses, clinical episodes and/or treatments.

Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence and EuroQoL.

Guide symptoms of a possible Lung Cancer will also be recorded:

A cough that does not go away or gets worse

Coughing up blood or rust-colored sputum (spit or phlegm)

Chest pain that is often worse with deep breathing, coughing, or laughing

Hoarseness

Loss of appetite

Unexplained weight loss

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Shortness of breath

Feeling tired or weak

Infections such as bronchitis and pneumonia that don't go away or keep coming back

New onset of wheezing

All these data will be entered in the Case Report Form (CRF) of the study and in the app developed by Bilbomática.

Final visit (24 months ± 2 months)

During the last visit (24 months from visit 1), clinical data and questionnaires will be recorded:

Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate

Spirometry result.

Medical record: New diagnoses, clinical episodes and/or treatments.

Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist and EuroQoL.

All these data will be entered in the Case Report Form (CRF) of the study.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification

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Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

b. Basque Country Clinical Site

7. CLINICAL MANAGEMENT AND STUDY PLAN

PHASE 1 study: General population screening: *Identify citizens with low to moderate risk of LC according to the developed risk factor assessment tools, suitable for further screening using low-cost devices in community-based settings or in centralized screening facilities.*

VISIT 1 - Baseline

Clinicians from the different clinical centers will identify possible participants from their consultations. These participants will be both smokers and never smokers & reduced smokers with low to moderate risk of Lung Cancer who meet the criteria generated by risk factor assessment tools.

Recruitment will ensure only eligible participants are included so that relevant and high-quality data is collected. Targets will be set to ensure research activities are delivered on time. All possible measures will be taken to ensure there is no discrimination or harms from the recruitment, exclusion or inclusion process.

On the first day of visit 1 or baseline, the principal investigators and their team of collaborators will review the eligibility of patients who meet the inclusion criteria and none of the exclusion criteria, established in sections 4.4.1 and 4.4.2.

Recruitment will be carried out by the main investigator and/or the co-investigators authorized to do so at the General Practitioner and/or pneumologist's consultation. The researcher will proceed to inform the selected patients about the possibility of participating in the clinical trial by explaining them what their participation will consist of through the Patient Information Sheet and the Informed Consent. The participants will be able to ask all the questions they deem appropriate in order to clarify all their doubts and will take the time they consider necessary to decide.

If the patient wishes to participate in the study, they will sign the Informed Consent and a code will be assigned to guaranty the pseudoanonymization of the patient and included in the participant's electronic health record (EHR).

The code will be as it goes:

LUCIA-XX-####

Being:

- **XX**: the code of the site where the patient has been recruited (AN for Andalusia, BC for Basque Country, LI for Liège and RI for Riga)

- **####:** the number of patient recruited (consecutive numbers in order of recruitment from 0001 to 1,000)

During this first visit, the principal investigator and/or their collaborators will access the EHR of each patient and will record the clinical data:

- Sociodemographic data: Age, Gender, Ethnicity, socioeconomic factors, deprivation index, education level.
- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
- Spirometry result.
- Medical record: Family history of lung cancer or other types of cancer, emphysema/ COPD (+GOLD classification)/ asthma, Interstitial Lung Disease (interstitial patterns), bronchiectasis, arterial hypertension, dyslipidemia, previous acute myocardial infarction, vasculopathies and chronic treatment.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence test and EuroQoL.
- Geo-location

All clinical sites will perform or use a standard of care (SOC) common blood test that will be enriched in each one of the sites as follows:[JEIU1]

Investigators will collect a blood sample of the participants for its analysis, including:

- General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Transferrin Index, Cholesterol, transferrin, phosphate, calcium
- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium, Urate
- Tumor markers: CEA, CA125, CYFRA 21.1, NSE
- General haematology: blood count, erythrocyte sedimentation rate

- Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

If abnormal values are observed after performing the blood analysis, the researcher in charge of the subject involved in the study will handle the situation according to usual clinical practice.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

All these data will be entered in the Case Report Form (CRF) of the study developed by Bilbomática.

The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.

Based on the assessment carried out by the results of the LDCT, the devices (individuals who show positive or uncertain results) and by established risk factor models, subjects will:

- Continue in **Phase 1: Wide population Screening** if low-moderate risk of lung cancer is assigned.
- Be referred to **Phase 2: Precision Screening** and included within polygenetic scoring analysis if high risk of lung cancer is assigned.
- Be referred to **Phase 3: Diagnosis** if by results of LDCT lung cancer or Indeterminate Pulmonary Nodules (IPN) are found.

Follow up visit 2 (6 months ± 30 days)

6 months after the beginning of the project an interim analysis of the recruited patients will be carried out to verify the heterogeneity of the sample and to ensure that we comply with the representativeness of each group in the study.

If the minimum percentage of subject per group is not achieved, the recruitment will follow in the misrepresented group until the balance is restored.

This visit will be performed remotely.

During this visit, the following information will be recorded:

- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

Follow up visit 3 (12 months ± 2 months)

During the follow up visits (12 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
- Spirometry result.
- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence and EuroQoL.

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

All these data will be entered in the Case Report Form (CRF) of the study and in the app developed by Bilbomática.

Final visit (24 months ± 2 months)

During the last visit (24 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate
- Spirometry result.
- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist and EuroQoL.

All these data will be entered in the Case Report Form (CRF) of the study.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification

- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project

c. Belgium Clinical Site

7. CLINICAL MANAGEMENT AND STUDY PLAN

PHASE 1 study: General population screening: *Identify citizens with low to moderate risk of LC according to the developed risk factor assessment tools, suitable for further screening using low-cost devices in community-based settings or in centralized screening facilities.*

VISIT 1 - Baseline

Clinicians from the different clinical centers will identify possible participants from their consultations. These participants will be both smokers and never smokers & reduced smokers with low to moderate risk of Lung Cancer who meet the criteria generated by risk factor assessment tools.

Recruitment will ensure only eligible participants are included so that relevant and high-quality data is collected. Targets will be set to ensure research activities are delivered on time. All possible measures will be taken to ensure there is no discrimination or harms from the recruitment, exclusion or inclusion process.

On the first day of visit 1 or baseline, the principal investigators and their team of collaborators will review the eligibility of patients who meet the inclusion criteria and none of the exclusion criteria, established in sections 4.4.1 and 4.4.2.

Recruitment will be carried out by the main investigator and/or the co-investigators authorized to do so at the General Practitioner and/or pneumologist's consultation. The researcher will proceed to inform the selected patients about the possibility of participating in the clinical trial by explaining them what their participation will consist of through the Patient Information Sheet and the Informed Consent. The participants will be able to ask all the questions they deem appropriate in order to clarify all their doubts and will take the time they consider necessary to decide.

If the patient wishes to participate in the study, they will sign the Informed Consent and a code will be assigned to guaranty the pseudoanonymization of the patient and included in the participant's electronic health record (EHR).

For the specific multi-omics study, either a separate and distinctive ICF will be available or a multi-choice section will be proposed in the ICF.

The code will be as it goes:

LUCIA-XX-####

Being:

- **XX**: the code of the site where the patient has been recruited (AN for Andalusia, BC for Basque Country, LI for Liège and RI for Riga)
- **####**: the number of patient recruited (consecutive numbers in order of recruitment from 0001 to 1,000)

During this first visit, the principal investigator and/or their collaborators will access the EHR of each patient and will record the clinical data:

- Sociodemographic data: Age, Gender, Ethnicity, socioeconomic factors, deprivation index, education level.
- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate.
- Spirometry result.
- Medical record: Family history of lung cancer or other types of cancer, emphysema/ COPD/ asthma, Interstitial Lung Disease (interstitial patterns), bronchiectasis, arterial hypertension, dyslipidemia, previous acute myocardial infarction, vasculopathies and chronic treatment.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence test and EuroQoL.
- Geo-location

All clinical sites will perform or use a standard of care (SOC) common blood test that will be enriched in each one of the sites as follows:

Andalusian Clinical Site: Investigators will collect a blood sample of the participants for its analysis, including:

- General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Cholesterol, transferrin, phosphate, calcium

- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium, Urate
- General haematology: blood count, erythrocyte sedimentation rate
- Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

Basque Country Clinical Site: Investigators will collect a blood sample of the participants for its analysis, including:

- General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Transferrin Index, Cholesterol, transferrin, phosphate, calcium
- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium, Urate
- Tumor markers: CEA, CA125, CYFRA 21.1, NSE
- General haematology: blood count, erythrocyte sedimentation rate
- Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

Belgian Clinical Site: Investigators will use data gathered through SOC, including but not limiting to variables (General overview of potential markers) combining mandatory and nice to have biological markers collected through SOC:

- General Biochemistry: C reactive protein, Proteins, Chloride
- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: Creatinine, Sodium, potassium, Urate

- General haematology: blood count
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of patients' enrollment and management of these blood samples are describe in section 8).

Latvian Clinical Site: Investigators will use data gathered through SOC, including but not limiting to variables (General overview of potential markers) combining mandatory and nice to have biological markers collected through SOC:

- Glucose, C reactive protein, Proteins, Albumin, Calcium
- Hepatic profile: GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium,
- General haematology: blood count, erythrocyte sedimentation rate
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of patient's enrollment and management of these blood samples are describe in section 8).

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

All these data will be entered in the Case Report Form (CRF) of the study developed by Bilbomática.

Andalusian Clinical Site: No CT scan will be performed.

Basque Country Clinical Site: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.

Belgian Clinical Site: If an acceptable (LD)CT image is available based on patient medical file from less than 12 months, it will be used for the study in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.

Latvian Clinical Site: No CT scan will be performed.

Based on the assessment carried out by the results of the (LD)CT (only for Basque Country and Belgium), the devices (individuals who show positive or uncertain results) and by AI analysis risk factor model, subjects will:

- Continue in **Phase 1: Wide population Screening** if low-moderate risk of lung cancer is assigned by AI analysis.
- Be referred to **Phase 2: Precision Screening** and included within polygenetic scoring analysis if high risk of lung cancer is assigned by AI analysis developed through the project. Depending of the model performance, patient can alternatively be selected on pre-specified risk factors.
- Be referred to **Phase 3: Diagnosis** if by results of (LD)CT lung cancer or Indeterminate Pulmonary Nodules (IPN) are found.

Follow up visit 2 (6 months ± 30 days)

6 months after the beginning of the project an interim analysis of the recruited patients will be carried out to verify the heterogeneity of the sample and to ensure that we comply with the representativeness of each group in the study.

If the minimum percentage of subject per group is not achieved, the recruitment will follow in the misrepresented group until the balance is restored.

This visit will be performed remotely.

During this visit, the following information will be recorded:

- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness

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- Loss of appetite
- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

Follow up visit 3 (12 months ± 2 months)

During the follow up visits (12 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate.
- Spirometry result.
- Medical record: new diagnosis, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence and EuroQoL.

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss

- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

All these data will be entered in the Case Report Form (CRF) of the study and in the app developed by Bilbomática.

Final visit (24 months ± 2 months)

During the last visit (24 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate.
- Spirometry result.
- Medical record: new diagnosis, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist and EuroQoL.

All these data will be entered in the Case Report Form (CRF) of the study.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

Andalusian Clinical Site: No CT scan will be performed.

Basque Country Clinical Site: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project

Belgian Clinical Site: If an acceptable (LD)CT image is available through SOC during visit follow up from less than 12 months, it will be used for the study in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project

Latvian Clinical Site: No CT scan will be performed.

d. Latvia Clinical Site

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7. CLINICAL MANAGEMENT AND STUDY PLAN

PHASE 1 study: General population screening: *Identify citizens with low to moderate risk of LC according to the developed risk factor assessment tools, suitable for further screening using low-cost devices in community-based settings or in centralized screening facilities.*

VISIT 1 - Baseline

Clinicians from the different clinical centers will identify possible participants from their consultations. These participants will be both smokers and never smokers & reduced smokers with low to moderate risk of Lung Cancer who meet the criteria generated by risk factor assessment tools.

Recruitment will ensure only eligible participants are included so that relevant and high-quality data is collected. Targets will be set to ensure research activities are delivered on time. All possible measures will be taken to ensure there is no discrimination or harms from the recruitment, exclusion or inclusion process.

On the first day of visit 1 or baseline, the principal investigators and their team of collaborators will review the eligibility of patients who meet the inclusion criteria and none of the exclusion criteria, established in sections 4.4.1 and 4.4.2.

Recruitment will be carried out by the main investigator and/or the co-investigators authorized to do so at the General Practitioner and/or pneumologist's consultation. The researcher will proceed to inform the selected patients about the possibility of participating in the clinical trial by explaining them what their participation will consist of through the Patient Information Sheet and the Informed Consent. The participants will be able to ask all the questions they deem appropriate in order to clarify all their doubts and will take the time they consider necessary to decide.

If the patient wishes to participate in the study, they will sign the Informed Consent and a code will be assigned to guaranty the pseudoanonymization of the patient and included in the participant's electronic health record (EHR).

For the specific multi-omics study, either a separate and distinctive ICF will be available or a multi-choice section will be proposed in the ICF.

The code will be as it goes:

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Being:

- **XX**: the code of the site where the patient has been recruited (AN for Andalusia, BC for Basque Country, LI for Liège and RI for Riga)
- **####**: the number of patient recruited (consecutive numbers in order of recruitment from 0001 to 1,000)

During this first visit, the principal investigator and/or their collaborators will access the EHR of each patient and will record the clinical data:

- Sociodemographic data: Age, Gender, Ethnicity, socioeconomic factors, deprivation index, education level.
- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate, respiratory rate.
- Medical record: Family history of lung cancer or other types of cancer, emphysema/ COPD (+GOLD classification)/ asthma, Interstitial Lung Disease (interstitial patterns), bronchiectasis, arterial hypertension, dyslipidemia, previous acute myocardial infarction, vasculopathies and chronic treatment.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence test and EuroQoL.
- Geo-location

All clinical sites will perform or use a standard of care (SOC) common blood test that will be enriched in each one of the sites as follows:

Andalusian Clinical Site: Investigators will collect a blood sample of the participants for its analysis, including:

- General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Cholesterol, transferrin, phosphate, calcium

- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium, Urate
- General haematology: blood count, erythrocyte sedimentation rate
- Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

Basque Country Clinical Site: Investigators will collect a blood sample of the participants for its analysis, including:

- General Biochemistry: Glucose, HDL Cholesterol, Iron, C reactive protein, Proteins, Albumin, LDL Cholesterol, Ferritin, Chloride, Lactate dehydrogenase (LDH), Triglycerides, Transferrin Index, Cholesterol, transferrin, phosphate, calcium
- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium, Urate
- Tumor markers: CEA, CA125, CYFRA 21.1, NSE
- General haematology: blood count, erythrocyte sedimentation rate
- Hemostasis: partial thromboplastin time, fibrinogen, international normalized ratio (INR), prothrombin time
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of management of these blood samples are describe in section 8).

Belgian Clinical Site: Investigators will use data gathered through SOC, including but not limiting to variables (General overview of potential markers) combining mandatory and nice to have biological markers collected through SOC:

- General Biochemistry: C reactive protein, Proteins, Chloride
- Hepatic profile: GOT, GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: Creatinine, Sodium, potassium, Urate
- General haematology: blood count

- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of patients' enrollment and management of these blood samples are describe in section 8).

Latvian Clinical Site: Investigators will use data gathered through SOC, including but not limiting to variables (General overview of potential markers) combining mandatory and nice to have biological markers collected through SOC:

- Glucose, C reactive protein, Proteins, Albumin, Calcium
- Hepatic profile: GPT, GGT, Bilirubin, Alkaline phosphatase
- Kidney profile: urea, Creatinine, Sodium, potassium,
- General haematology: blood count, erythrocyte sedimentation rate
- Omics analysis based on blood samples: patients will also be asked to participate in the specific OMICS sub-analysis evaluating genetic and epigenetics modifications. (Specifications of patient's enrollment and management of these blood samples are describe in section 8).

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

All these data will be entered in the Case Report Form (CRF) of the study developed by Bilbomática.

Andalusian Clinical Site: No CT scan will be performed.

Basque Country Clinical Site: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.

Belgian Clinical Site: If an acceptable (LD)CT or CT image is available based on patient medical file from less than 12 months, it will be used for the study in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the beginning of the project.

Latvian Clinical Site: No CT scan will be performed.

Based on the assessment carried out by the results of the (LD)CT (only for Basque Country and Belgium), the devices (individuals who show positive or uncertain results) and by established risk factor models, subjects will:

- Continue in **Phase 1: Wide population Screening** if low-moderate risk of lung cancer is assigned.
- Be referred to **Phase 2: Precision Screening** and included within polygenetic scoring analysis if high risk of lung cancer is assigned by AI analysis developed through the project. Depending of the model performance, patient can alternatively be selected on pre-specified risk factors.
- Be referred to **Phase 3: Diagnosis** if by results of (LD)CT lung cancer or Indeterminate Pulmonary Nodules (IPN) are found.

Follow up visit 2 (6 months ± 30 days)

6 months after the beginning of the project an interim analysis of the recruited patients will be carried out to verify the heterogeneity of the sample and to ensure that we comply with the representativeness of each group in the study.

If the minimum percentage of subject per group is not achieved, the recruitment will follow in the misrepresented group until the balance is restored.

This visit will be performed remotely.

During this visit, the following information will be recorded:

- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss

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- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

Follow up visit 3 (12 months ± 2 months)

During the follow up visits (12 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate.
- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist, Mediterranean diet adherence and EuroQoL.

Guide symptoms of a possible Lung Cancer will also be recorded:

- A cough that does not go away or gets worse
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back

- New onset of wheezing

All these data will be entered in the Case Report Form (CRF) of the study and in the app developed by Bilbomática.

Final visit (24 months ± 2 months)

During the last visit (24 months from visit 1), clinical data and questionnaires will be recorded:

- Physical exploration: Height, Weight, Body Mass Index (BMI), blood pressure, heart rate
- Medical record: New diagnoses, clinical episodes and/or treatments.
- Exposure to harmful agents: smoking and occupational exposure (physical activity and frequency, alcohol intake, cigarette packets/year, age of smoking onset, time elapsed since last cigarette, occupational exposure to carcinogens).

The participant will have to complete the following questionnaires, which will be collected and filed as part of the participant's information:

- Lifestyle and Quality of Life (QoL) questionnaires: HPLP-II, Fantastic lifestyle Checklist and EuroQoL.

All these data will be entered in the Case Report Form (CRF) of the study.

Professionals will guide participants in the use of the non-invasive portable devices studied in this assay:

- Breath Analyzer (BAN): Collection of a breath sample for biomarkers identification
- Spectrometry-on-Card (SPOC): Collection of a 3-5mL of blood sample or biomarkers identification

Andalusian Clinical Site: No CT scan will be performed.

Basque Country Clinical Site: The clinician will make an appointment for a Low Dose Computerized Tomography (LDCT) in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project

Belgian Clinical Site: If an acceptable LDCT or CT image is available through SOC during visit follow up from less than 12 months, it will be used for the study in order to verify the lack of pulmonary nodules or lung cancer disease in the patient at the end of the project.

Latvian Clinical Site: No CT scan will be performed.