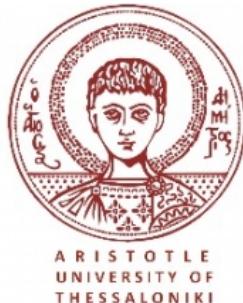


Aristotle University of Thessaloniki

Biomedical Engineering Department



Expert System TNM Classification of Malignant Tumors Lung Cancer

This report is submitted in partial fulfillment of the requirement for the course Artificial Intelligence and medical diagnosis decision support systems.

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Expert System

TNM Classification of Malignant Tumors

Lung Cancer

Abstract

There are numerous different diseases that are extremely difficult to diagnose at present. Lung carcinoma is a disease of this category. It travels from the lungs to other organs in the human body. It can develop in any area of the airways and is typically caused by smoking or chemical exposure. Expert systems, also known as decision support systems, are artificial intelligence systems that have been trained to execute complex tasks such as the diagnosis of lung cancer. A variety of medical expert systems tools are available and can serve as intelligent assistants to clinicians, assisting with diagnostic procedures, laboratory analysis, treatment protocol, and the instruction of medical students and residents. A model for computer-based medical diagnosis of primary immunodeficiencies is also presented. In this paper, we describe the design and implementation of an expert system that can assist clinicians in diagnosing lung cancer and selecting the optimal treatment.

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Chapter 1

Introduction

The purpose of this project is the construction of an expert system (ES) that investigates the stage of patients with lung cancer. The ES has the following attributes:

- **Agent Type:** Medical diagnosis system
- **Performance Measure:** Healthy patient, reduced costs
- **Environment:** Patient, hospital, staff
- **Actuators:** Display of questions, tests, diagnoses
- **Sensors:** Keyboard entry of patient's symptoms

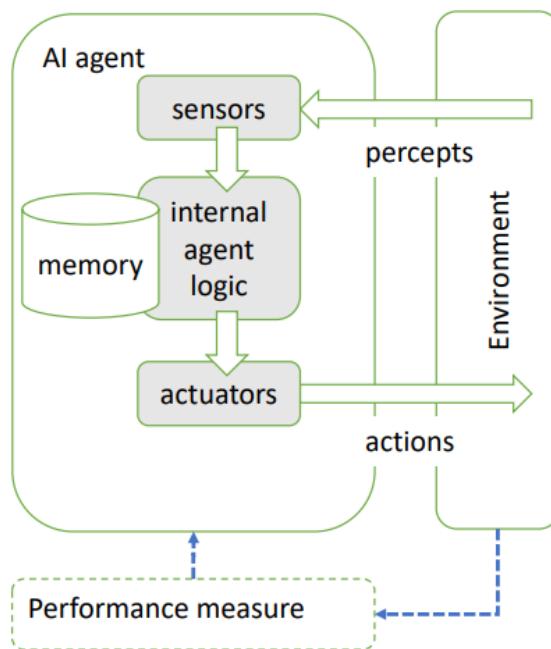


Figure 1.1: Expert System Attributes

The diagnostic process requires iterative usage of the aforementioned sensors and actuators, with the agent's internal logic mediating the evaluation of the data. The process needs to be evaluated in terms of:

- Its accuracy, which for this context means how often the agent can infer the TNM cancer stage using the predefined rules.
- The overall estimated time from initial subject examination until the estimation of the cancer stage using the TNM methodology
- The overall cost for the medical examinations that were needed for the agent to infer the TNM cancer stage.

Chapter 2

Background

2.1 Lung Cancer

The lungs are a component of the respiratory system that helps you breathe. The primary function of the respiratory system is to bring fresh oxygen into the body while removing waste gases. Lung cancer is a form of cancer , which in most cases concerns, what is known as brochial carcinomas. Bronchial carcinomas arise from the respiratory epithelium. The respiratory epithelium is a layer of epithelial cells with specified cila which are very helpful for the filtration of air. The respiratory mucosa, as it is called, functions as an organ which consists of respiratory epithelium and the lamina propria, a layer of connective tissue upon which lay the epithelial cells. The epithelium can create formations, which produce mucus and help in the protection of the airways from microbes, and they are named glands. From these specific cells arise the formation and dysplastic procedures and more specifically from the basal cells of the epithelium, which are found in the lower 1/3 of the epithelium. Later the dysplasia extends in the whole width of the epithelium and since the dysplastic cells do not spread beyond the lamina propria and they do not infiltrate lymph and blood vessels, the dysplasia of this stage is called *in situ* carcinoma. The kind of the epithelium which can be found along the airways can differ, since in the terminal portions of the respiratory system, where the alveoli can be found, the epithelium is squamous and single-layer. From this kind of the epithelium arises the squamous cell carcinoma, whether from the glandular epithelium the ,so called , adenocarcinoma. A special type is the carcinoma from large cells. (Carneiro, 2011). These are the non-small cells lung cancers (NSLCS) and they are called so , in order to be separated from the small cell lung carcinoma, a rarer and more aggressive cancers, with different traits from the NSCLCs, histologically and clinically. [2]

2.1.1 Types of lung cancer

Lung cancer that originates in the airways is known as primary lung cancer. Secondary lung cancer refers to cancer that has migrated to the lungs from another area of the body. There are two major types of primary lung cancer, which are distinguished by the type of cells from which the cancer originates: [13]

- **Non-small-cell lung cancer**
- **Small-cell lung cancer** Further classification of the lung cancer types is: 1) small cell lung carcinoma 2) squamous cell carcinoma 3) adenocarcinoma 4) lung can-

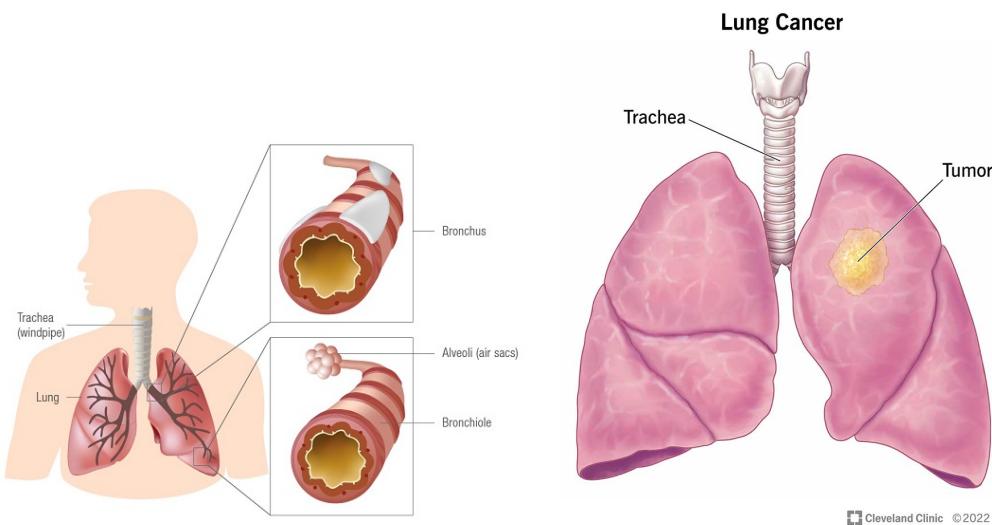


Figure 2.1: Typically, lung cancer begins in the airways (bronchi or bronchioles) or air sacs (alveoli) of the lungs. [10]

cer with big cells. The three last cases of lung cancer are classified as non-small cell lung carcinoma. As far as the SCLC is concerned, it can be 15% of lung cancer incidents and it is located in the 95% of the cases centrally near the pulmonary hilla. It can often lead to haematogenous metastases and infiltrations of organs such as, brain, bone marrow, liver and it can also cause a pleural effusion. It can cause signs of paraneoplastic syndrome since it is related to ectopic secretion of ACTH and Cushing syndrome, PTH-related peptide and hypercalcemia, ADH and SIADH, myasthenic syndrome of Lambert-Eaton and hypercoagularity. The hypercalcemia can also be attributed to bone metastases. Squamous cell carcinoma concerns the 20-25% of the lung cancer cases. It is mostly located centrally. It is mostly related to ectopic secretion of PTH-related peptide and hypercalcemia, as well as to hypercoagularity states. Adenocarcinoma is 50-60% of lung cancer cases and it can be found to non-smokers female patients. It is located peripherally and it leads very often to lymph nodes infiltration and haematogenous metastases mostly to bones, brain and liver. The lung cancer type with big cells is mostly a neuroendocrine type of cancer, which can be found positive to histological exams with chromogranin-A and neuron specific enolase (NSE). (Casaliato and Territo, 2012).

2.1.2 Epidemiology

Lung cancer is typically caused by smoking or exposure to secondhand smoke or passive tobacco smoke, but it can also be caused by a genetic mutation. A number of risk factors increase the likelihood of developing lung cancer. Some risks are controllable, whereas others are not. [11, 13] Smoking is associated with the 85-90% of lung cancer cases worldwide. The risk for a smoker compared to a non-smoker can be even 30 times higher. A very efficient limit, which can be applied in statistical studies over the relation between smoking and lung cancer can be the 10 packets/year. The packet year unit can be very useful for the estimation of the general amount of cigarettes that a patient has smoked through many years. For example 10 packets per year means either 1 packet per day for 10 years or 2 packets per day for 5 years, as it is calculated by multiplying the number

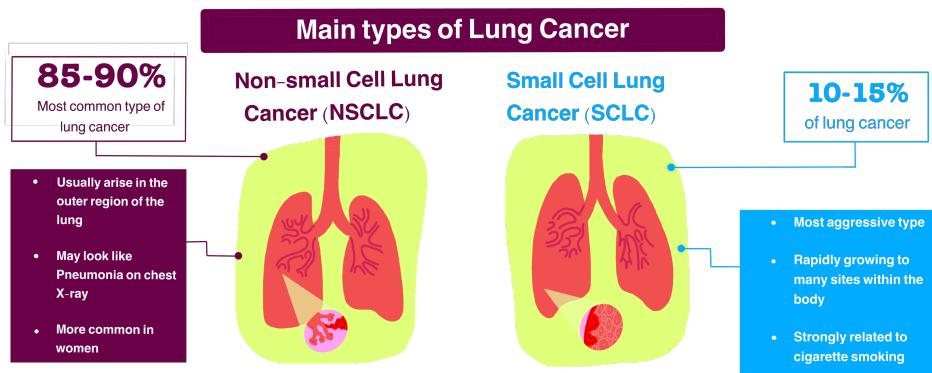


Figure 2.2: Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main types of lung cancer. [3]

of packets which are smoked per day and the number of years for which the patient has been a smoker. Over the 10 packet years, there is an increase of the incidence of deaths by lung cancer. Additionally the passive smoking has been related to lung cancer cases. It is estimated that the passive smoking can double the risk to non smokers for lung cancer. The absence of smoking from the patient's history can be related only to a few cases of adenocarcinoma, which can appear to non-smokers female patients. It excludes the possibility for small cell lung carcinoma (SCLC). (Casaliato and Territo, 2012). The exposure to asbestos must lead to the suspicion for mesothelioma, a type of pleura cancer, as the 80% of mesothelioma cases can be associated with history of asbestos exposure. Thus the sensitivity of chronic asbestos exposure for mesothelioma is 80%. The exposure to radionucleotides is another factor, which must be taken under suspicion for lung cancer, since 6% of the cases are attributed to exposure to radionucleotides. COPD can be another risk factor for lung cancer. The history of neck and head cancer can be also a risk factor as part of the cancerization effect. (Davidson, 2012).smo

2.1.3 Symptoms of lung cancer

Depending on where and how widely the cancer cells have spread, the signs and symptoms of lung cancer vary, and in some cases, the disease may not produce any pain or other symptoms. The lung cancer can be divided, generally, in three subtypes, depending on their origin. The symptoms of the primary tumor are the most common and the most important. They include:

- chest pain
- haemoptysis
- dyspnea
- productive or dry cough in many cases
- hoarseness
- compressing symptoms from nearby anatomical structures such as trachea, esophagus, mediastinum, pleura and laryngeal nerve.

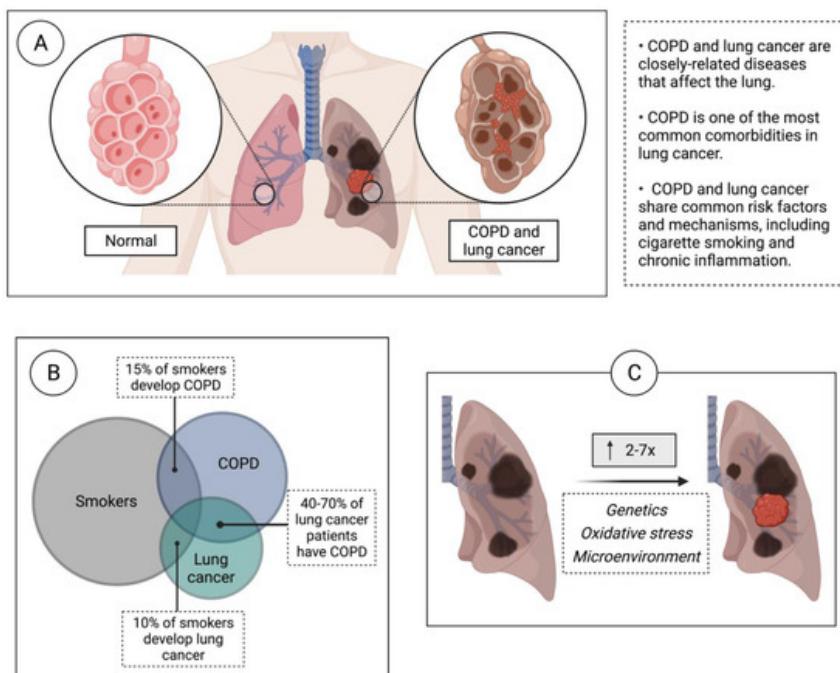


Figure 2.3: Enter Caption

Furthermore, there are the symptoms from metastases and the systemic symptoms such as:

- weight loss
- bone pain
- automatic bone fracture

Finally, there are symptoms which are related to some rarer manifestations of lung cancer, when the tumor secretes hormones such as ACTH, ADH, autoantibodies and serotonin. These secretions can demonstrate functional and endocrinological symptoms from other systems and they are classified as paraneoplastic syndrome.

2.1.4 Diagnosis of lung cancer

A combination of imaging tests and a biopsy of an area of aberrant growth detected on a scan or during a physical examination are used to diagnose lung cancer. After validating a lung cancer diagnosis, additional tests may be conducted to determine if the cancer has spread to other areas of the body. [2]

1. **The diagnosis is based, first of all, on the history of the patients and the symptoms, which are presented.** The symptoms can be distinguished in three large categories. On the first category, are classified the symptoms of the primary tumor. In this category belong symptoms such as dyspnea, haemoptysis, chest pain, productive or dry cough, symptoms from bronchial plexus and symptoms of Horner syndrome, both of them in case of tumor, which is located on the pulmonary apex. On the second category, there are found metastatic symptoms such as weight loss, bone

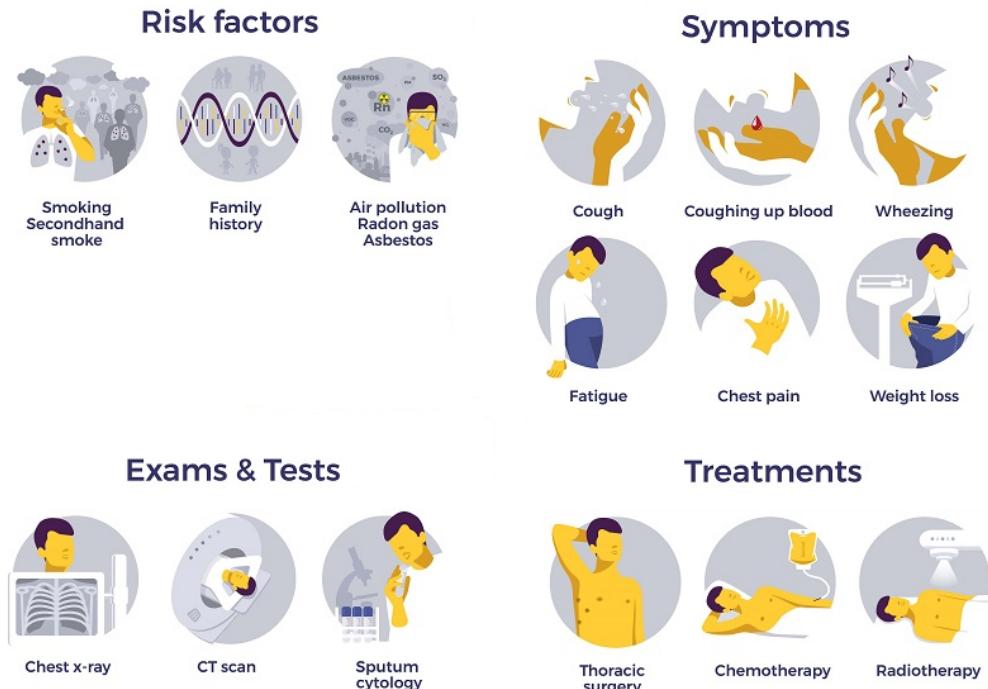


Figure 2.4: Risk factors and symptoms of lung cancer.

pains, automatic fractures and liver dysfunction. Finally on the third category belong the paraneoplastic symptoms. The paraneoplastic syndrome can be demonstrated with high ACTH secretion and Cushing syndrome, with moon-shaped face, osteoporosis, hypertension, central obesity, proximal myopathy and hyperglycemia. Additionally, it can be demonstrated with high ADH secretion and SIADH, with hyponatremia, neurologic symptoms and peripheral edema. In case of secretion of PTH-related peptide, the patient can present with hypercalcemia, which causes constipation, neurologic symptoms, QT-shortening, bradycardia, hypertension, nausea, vomiting, diabetes insipidus, nephrolithiasis, lethargy, AV block, pancreatitis, peptic ulcer and depression. Paraneoplastic syndrome is related to hypercoagularity states and myasthenic syndrome of Lambert-Eaton, which is associated almost completely with SCLC. In this syndrome, the tumor produces autoantibodies against the Ca vesicles of the presynaptic neurons, which causes decrease of acetylcholine release from the presynaptic neuron and leads to severe neurologic symptoms.

2. **On physical examination**, it is expected to be found decreased pulmonary sounds, wheezing and ronchi, palpable, hard and painless supraclavical, cervical or axillary lymph nodes, hepatomegaly on abdominal palpitation and skin nodules, which can indicate distal metastases.
3. **On the laboratory exams**, there can be found on CBC low Hb/Hct, low WBCs, low Plts, all of whom indicate bone marrow infiltration. Elevated values of transaminases , γ -GT, ALP, bilirubin, PT, INR and low values of albumin indicate liver damage and possible metastases. The possibility of metastases is higher , in case of kidney injury, which is demonstrated by elevated values of urea and creatinine. Elevated ALP is for bone metastases except of liver metastases. Elevated LDH indicates bone marrow infiltration, elevated potassium, phosphorus and uric acid demonstrate possible tumor lysis syndrome and elevated calcium indicates either

bone metastases or paraneoplastic syndrome.

Imaging tests

1. **Chest X-ray:** Chest X-rays are used to identify abnormalities in the lungs, which can then be examined further with a CT scan. A chest X-ray can be valuable in lung cancer diagnosis because of the possible imaging of a mass or other infiltrations, which can raise the suspicion for a tumor. In any case, a patient with the above symptoms is always a candidate for a chest X-ray, not only in order to investigate or detect findings of a tumor, but also to exclude other possible diagnosis such as a pneumonia or a pneumothorax.
2. **Computerized Tomography (CT) Scan:** CT scans use x-ray beams that are rotated around the body to generate a series of images that produce a complete image of the body part being scanned. A CT scan can provide information regarding the size, shape, and location of lung tumors. In addition, it can help detect areas where the cancer may have spread, such as the lymph nodes between the lungs or in the neck, or organs such as the adrenal glands, liver, and brain. This is the basic examination, which the patient must be undergone because of its high specificity in the diagnosis of lung cancer. It can provide information about the anatomical position and the size of the tumor, additionally to the estimation of nearby anatomical structures, which may have been infiltrated and lymph nodes, which are not possible to be palpated such as mediastinal and hilar lymph nodes.

Pathologoanatomical investigation

1. **Bronchoscopy:** A thin, flexible fibre-optic tube called a bronchoscope is passed through the nose or mouth, down the trachea into the lungs so that a sample (biopsy) can be taken. It is a test through which it is possible to take biopsies with a needle through the airway wall, something that much easier in case of a centrally located or perihilarly located tumor.
2. **Needle Biopsy:** A needle may be used to obtain a sample (biopsy) from the area of abnormal growth. This could include samples from swollen lymph nodes in the neck or from parts of the lungs. In a transthoracic needle biopsy, a needle is guided via CT scan through the skin and into the area to remove a small sample for testing. The same examination can be conducted, when there are lymph nodes, which are considered dangerous on the physical examination of the patients.

Stage evaluations tests

1. **Bone Scan:** A bone scan can detect whether lung cancer has spread to the bones. In this procedure, a tiny amount of radioactive material known as a tracer is injected, and a scan is performed to determine how the tracer is absorbed, as this can indicate the presence of bone cancer spread.
2. **Positron Emission Tomography (PET) Scan:** A radioactive glucose solution is injected into the body during a PET scan. This is absorbed by rapidly dividing cells in the body, indicating the potential presence of cancer in these areas. Using a

specialized camera, the areas of glucose uptake can be identified, thereby revealing areas of active growth.

3. **Magnetic Resonance Imaging (MRI) Scan:** Similar to computed tomography (CT) scans, MRI scans provide detailed images of the body and are typically used to detect the spread of lung cancer to the brain or spinal cord. Instead of x-rays, MRI examinations use radio waves and powerful magnets to produce images.



Figure 2.5: A pathway map of a lung cancer diagnosis journey.

2.1.5 Staging of lung cancer

Small-cell lung cancer is less common than non-small-cell lung cancer. The cancerous cells are smaller in size than the cells that cause non-small-cell lung cancer and has only two possible stages: [13]

- **Limited disease:** where the cancer is only in one lung and may be in nearby lymph nodes
- **Extensive disease:** where cancer has spread to the other lung, to lymph nodes that are further away, or to other parts of your body

Non-small cell lung cancer is the most prevalent form of lung cancer, and its phases include the following: [1]

- **Stage 1:** a small portion of the lung is infected, but the disease has not progressed beyond the lungs.
- **Stage 2:** cancer has thoroughly infected the lungs and spread to nearby lymph nodes.
- **Stage 3:** cancer has spread to the lungs and lymph nodes in the center of the thorax.
- **Stage 3A:** cancer has spread to all lymph nodes on the side of the thorax where it originated.
- **Stage 3B:** cancer spreads from lymph nodes on the opposite side of the thorax to lymph nodes above the collarbone.
- **Stage 4:** cancer spreads to the lungs and the area surrounding the lungs and then to other organs.

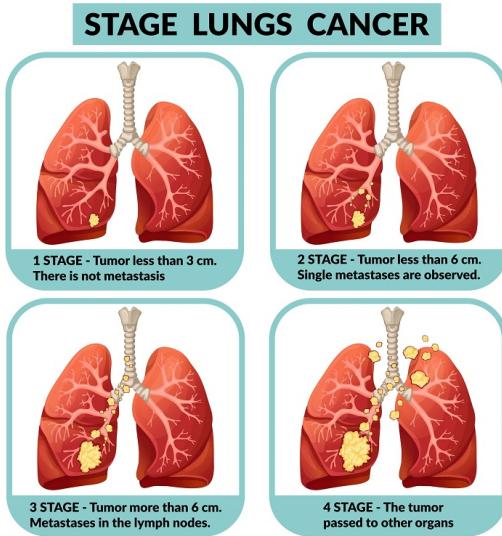


Figure 2.6: Stages of lung cancer. [1]

TNM classification

Clinicians use a staging system for lung cancer called TNM, where [13]. The TNM classification is applied mostly in case of NSCLC. This system predicts critical values for the tumor size, classifies differently the existence of tumors in some specific anatomical areas and reclassifies the pleural effusions as metastatic substage.

- **T** describes the **size of the tumour** (cancerous tissue) The radiologic investigation includes the classical chest X-ray and the chest-CT. On the chest X-ray there can be depicted a mass, infiltrations or no specific findings for tumor. If a mass is depicted, it has to be evaluated according to the location of the tumor. If the tumor is located centrally, it is for squamous cell carcinoma and SCLC and if it is located peripherally, it is for adenocarcinoma. In any case of findings, it is necessary, a further investigation to be conducted by a chest CT. On the chest CT there will be a more specific depiction of the tumor, if it exists. The size and the precise location of the tumor can be evaluated, as well as, the possible infiltration of pleura, mediastinum, or further nearby organs and tissues. In case of a single nodule, which has to fulfill the following traits, size less than 6cm, peripheral location, absence of findings from the physical, laboratory and radiological examination and asymptomatic patient, then additional investigation is required with FNA biopsy and PET-scan.
- **N** describes the **spread of the cancer into lymph nodes** The final examination in order not only to define the type of the tumor, but also to certificate the diagnosis , is the pathologic examination. The cytologic examination of sputum can be very useful since it has sensitivity 60-80% for centrally located tumor and 15-25% for peripherally located tumor. It has to be followed by bronchoscopy, an examination, during which FNA biopsy can be done transbronchially , if the tumor is located centrally or around the pulmonary hilum.
- **M** describes **whether the cancer has spread to another area of the body** such as the liver (metastasis) Further investigation is required in order to define the possibility for lymph nodes infiltration. The most indicative examination, which will

assure this suspicion, is the chest-CT, where if the mediastinal or hilar or peribronchial lymph nodes are found in size more than 1.5cm they are pathological, if they are less than 0.5cm they are normal and if they are 0.5-1.5cm they are considered undefined. In case of palpable, peripheral lymph nodes, without infective causes and enlarged for more than 4 weeks, a FNA biopsy must be conducted. For distal metastases the examination, which can be done include PET-scan of the whole body, CT or MRI of brain, abdominal CT, spinal MRI, scintigraphy of bones, X-ray of bones in painful anatomical areas.

T1	- lung cancer means that the cancer is still inside the lung	N1	- used to describe cancerous cells in the lymph nodes located inside the lung or in the area where the lungs connect to the airway (the hilum).
T1a	- the tumour is no wider than 1cm	N2	- there are cancerous cells in the lymph nodes located in the center of the chest on the same side as the affected lung, or - there are cancerous cells in the lymph nodes underneath the windpipe
T1b	- the tumour is between 1cm and 2cm wide	N3	- there are cancerous cells in the lymph nodes located on the chest wall on the other side of the affected lung, or - there are cancerous cells in the lymph nodes above the collar bone, or - there are cancerous cells in the lymph nodes at the top of the lung
T1c	- the tumour is between 2cm and 3cm wide		
T2	- the tumour is between 3cm and 5cm wide, or - the tumour has spread into the main airway or the inner lining of the chest wall, or - the lung has collapsed or is blocked due to inflammation		
T3	- the tumour is between 5cm and 7cm wide, or - there is more than 1 tumour in the lung lobe, or - the tumour has spread into the chest wall, the phrenic nerve (a nerve close to the lungs), or the outer layer of the heart (pericardium)		
T4	- the tumour is wider than 7cm, or - the tumour has spread into both sections of the lung (each lung is made up of 2 sections, known as lobes), or - the tumour has spread into an area of the body near to the lung, such as the heart, the windpipe, the food pipe (oesophagus) or a major blood vessel	M0	- the cancer has not spread outside the lung to another part of the body
		M1	- the cancer has spread outside the lung to another part of the body

Figure 2.7: TNM classification for lung cancer.

2.2 Expert Systems

An expert system (ES) is a knowledge-based system that employs domain-specific knowledge and an inference procedure to solve problems that might otherwise demand human capacity or expertise. The knowledge contained in the knowledge base of an expert system is the main component of its effectiveness. [4] Expert systems are generally meant to work with human experts, not to replace them. [8]

2.2.1 Architecture of an expert system

An expert system is made up of three parts:

- **User interface:** is the system that enables a non-expert user to query and receive advice from an expert system.
- **Knowledge base:** is a collection of facts and rules that are provided by human specialists.
- **Inference engine:** searches the knowledge base for information that matches the user's inquiry like a search engine.

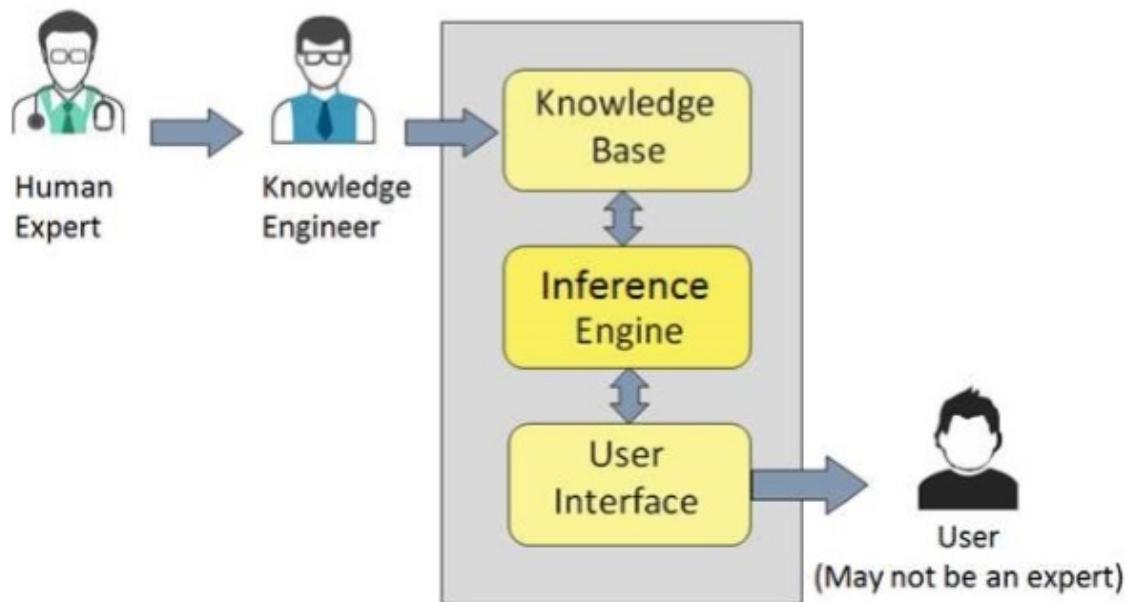


Figure 2.8: The expert system is queried by the non-expert user. This is accomplished by submitting a query or responding to questions posed by the expert system. The inference engine searches the knowledge base using the user's query and then returns an answer or recommendation.[5]

Knowledge Base

The data is a collection of facts. The information is organized as task-related data and facts. The knowledge base is a type of storage that stores knowledge acquired from the different

experts of a particular domain. Knowledge representation is the method for organizing and formalizing the knowledge in a knowledge base in the form of IF-THEN-ELSE rules.

Inference engine

The inference engine is referred to as the expert system's brain because it is the primary processing element. It applies rules of inference to the knowledge base to derive a conclusion or deduce new information. [6] The Inference Engine employs the following strategies to suggest a solution:

- **Forward Chaining:** begins with the known facts and rules, then applies the inference rules to the known facts in order to reach their conclusion.

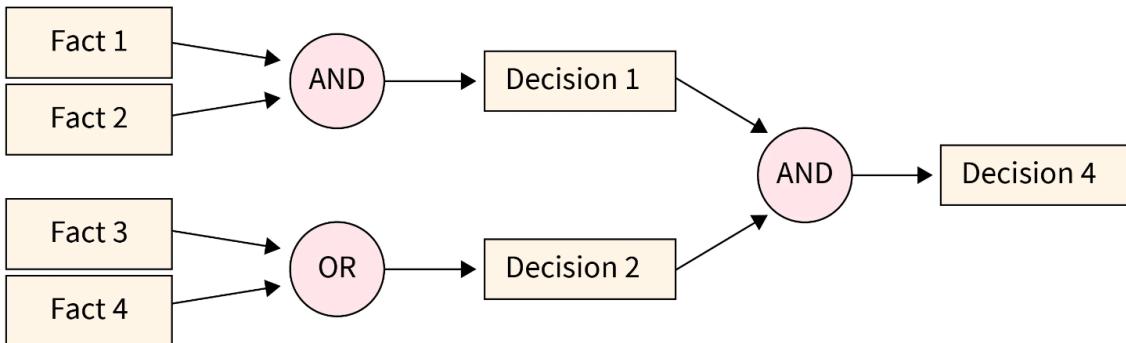


Figure 2.9: Forward Chaining

- **Backward Chaining:** is a method of reasoning that begins with the conclusion and proceeds backwards to prove the known facts.

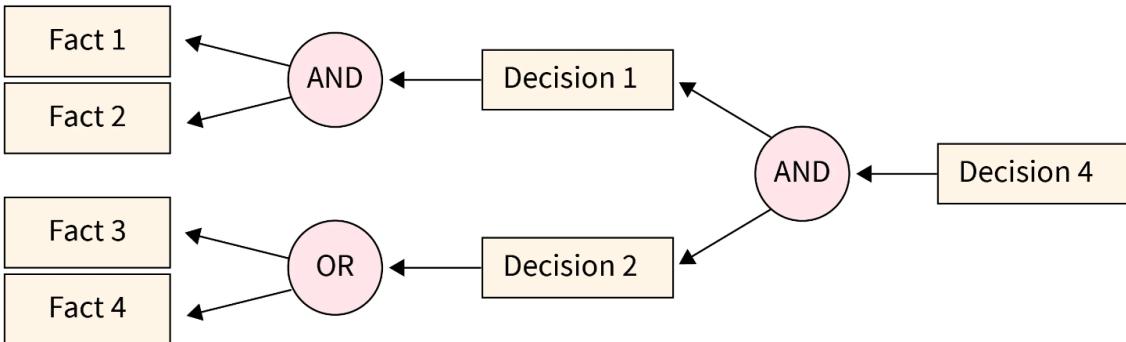


Figure 2.10: Backward chaining

2.2.2 Applications

Classification, diagnosis, monitoring, process management, design, scheduling, planning, and the production of options are all broad areas where ES has found use. [4]

- **Diagnosis Systems:** infer malfunction or disease from observable data
- **Classification:** identify an object based on given characteristics
- **Planning:** develop or modify a plan of action

- **Generation of Options:** create alternative solutions to a problem

Some examples of experts systems in the healthcare domain are the following: [9]

- **MYCIN** is a pioneering example of a backward chaining-based expert system. It can detect pathogenic germs that can lead to life-threatening infections and provide medicine recommendations based on body mass index.
- **PXDES** could quickly analyze the information to identify the kind and stage of lung cancer in a patient.
- **Clinical Decision Support System (CaDet)** used for early cancer detection in patients.
- **DXplain** is a diagnostic tool and a clinical support system that could make diagnoses based on the doctor's findings.

Chapter 3

Methodology

An Expert System is a smart computer tool that can act like a human expert when it comes to solving problems. Human knowledge includes both domain information and knowledge about how to solve problems. So, an expert system is a computer tool that represents what an expert in a certain field knows. Below are some of the most essential characteristics of an expert system:

- Operates on a specific domain
- Process incomplete information
- Process alternative solutions
- Provide reasons for the answer

3.0.1 Expert System Shells

It is recommended to use an expert system shell to save both time and effort in order to make the construction of expert systems as simple as possible. An expert system shell, often known as an ES Shell, is made up of some built parts of an expert system and an information base that is empty. The Expert System Shell is a piece of software that has an: [12]

- User interface is integrated
- Inference engine is integrated
- Empty structured knowledge base

where the knowledge base in ES shells, can be represented in the form of :

- as rules
- as objects
- in the form of a decision tree

3.0.2 Usage of Expert System Shells

ES-Builder

ES Builder stands for Expert System Builder. It is among the most well-known Expert System Shells. It is a free ES shell designed for students and researchers to create expert system shells.

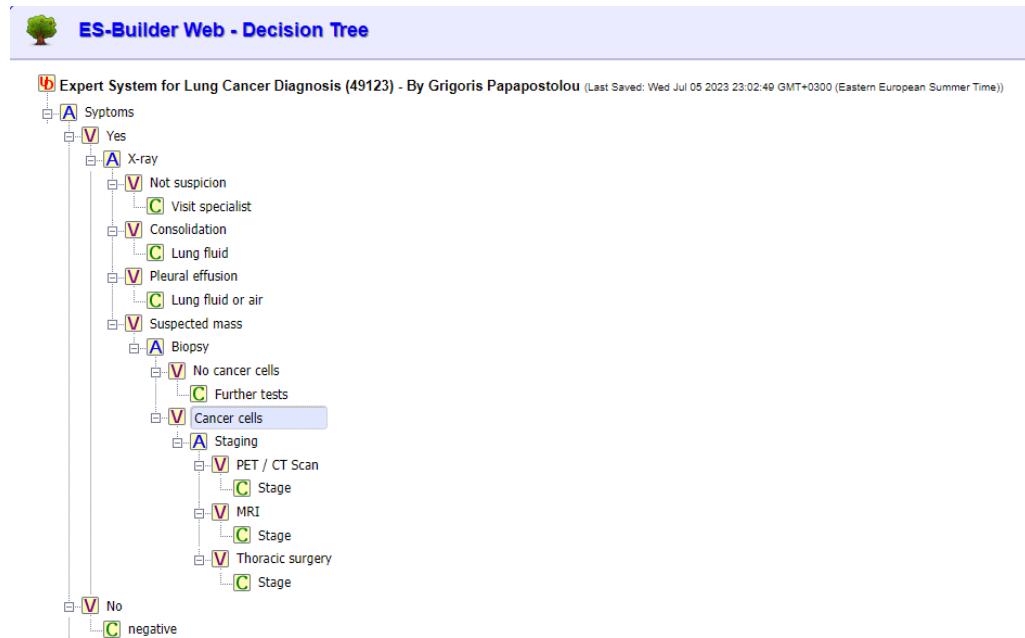


Figure 3.1: Example of ES Builder

The rule base knowledge base can be created using a decision tree that consists of:

- **Attribute:** are characteristics of possible conclusions that are to be tested
- **Value:** represents the response to an Attribute
- **Conclusion:** The final decision made based on the attributes and values

PyKE

PyKE is the abbreviation for Python Knowledge Engine. PyKE employs Prolog-inspired logic programming, but is written in the Python. The primary characteristics of the PyKE knowledge base are the python functions, PyKE rules, PyKE pattern variables, and graph plans. This is an inference engine that employs rules and facts to generate additional facts by forward chaining rules in order to prove objectives.

ExpertA

An expert system is a computer program that can match a set of data with a set of rules and take action based on the matching rules. [7]

Facts

ExpertA's fundamental unit of information is the fact. They are utilized by the system for problem reasoning. You can subclass Fact to express various types of data or extend its functionality with your own code.

```
class TUMOR_FACTS(Fact):
    mass = Field(bool, mandatory=True) # mass found with x-rays
    diameter = Field(float, mandatory=False) # diameter determined with ct-scan
    bronchoscopy = Field(bool, mandatory=False) # bronchoscopy examination as part of pathologoanatomical examination
    cytologic = Field(bool, mandatory=False) # cytologic examination as part of pathologoanatomical examination
    nearby_organs = Field(bool, mandatory=False) # infiltration of nearby organs found with ct-scan
    fna_and_pet_scan = Field(bool, mandatory=False) # the results of these two should always agree
```

Figure 3.2: Fact example

Rules

A rule in ExpertA is a function and consists of the following elements:

- **LHS (left-hand side)** describes (using patterns) the conditions under which the rule should be executed (or triggered). Logic operators can be used to convey complex LHS conditions.
- **RHS (right-hand side)** is the collection of actions to execute when the rule is executed.

```
class TumorStage(KnowledgeEngine):
    @Rule(TUMOR_FACTS(mass=False, diameter=P(lambda x: x==0), bronchoscopy=False, cytologic=False, nearby_organs=False, fna_and_pet_scan=False))
    def rule_tumor_t0(self):
        global var_tumor
        var_tumor = 'T0'

    @Rule(OR(TUMOR_FACTS(mass=False, diameter=P(lambda x: x==0), bronchoscopy=False, cytologic=True, nearby_organs=False, fna_and_pet_scan=False),
            TUMOR_FACTS(mass=False, diameter=P(lambda x: x==0), bronchoscopy=True, cytologic=False, nearby_organs=False, fna_and_pet_scan=False)))
    def rule_tumor_tx(self):
        global var_tumor
        var_tumor = 'Tx'

    ...
```

Figure 3.3: Rule example

Knowledge Engine

The Knowledge Engine applies the knowledge to the data.

3.0.3 Project-specific details

This section presents project-related key information, regarding the core of the agent, its components, the entities of its environment, how they communicate with each other, how synthetic data were generated and how the logging of the experiments is performed.

Agent

The AI Agent is the core part of an Expert System, in other words it is the non-human system which consists of Sensors, Actuators and the Internal Logic part, which is designed to provide support to a human expert to take a decision about a Subject, whether it is an exam order or a diagnosis.

The agent used for the implementation of our project is of Simple Reflex Agent (SRA) type, meaning its core consists of rules and facts that the engine uses to infer an action, contrary to other types of expert systems that make use of Machine Learning (ML) models to infer their actions. An SRA is an agent that selects actions based on the current percept (input), ignoring the rest of the percept history. It uses condition-action rules (if-then rules), which directly map states to actions. The main difference in the way an SRA works compared to more complex agents is that it's deterministic in its nature, given that for the same input the output will always be the same, whereas the ML based agents are stochastic. That characteristic of how an SRA works, apart from the difference in its structure, also affects what the performance measurement means for such an agent.

For an SRA agent to be able to reach a conclusion it needs information for all the defined properties of the relevant facts. This is due to the fact that if not all information is available then most probably no rule will be able to fire. Of course, there are a few works around solutions which include for example custom solutions that could record the closest related rule or adding default rules at the end of each knowledge engine using the salient property, but none of these solutions is considered a good practice. The deterministic nature of SRA agents also affects the way we measure the agent's performance. Given that such an agent would always return the same output for the same input. What really is at stake is, if the prerequisites of a Rule align with the actual symptoms of someone who suffers from the disease that the rule corresponds to.

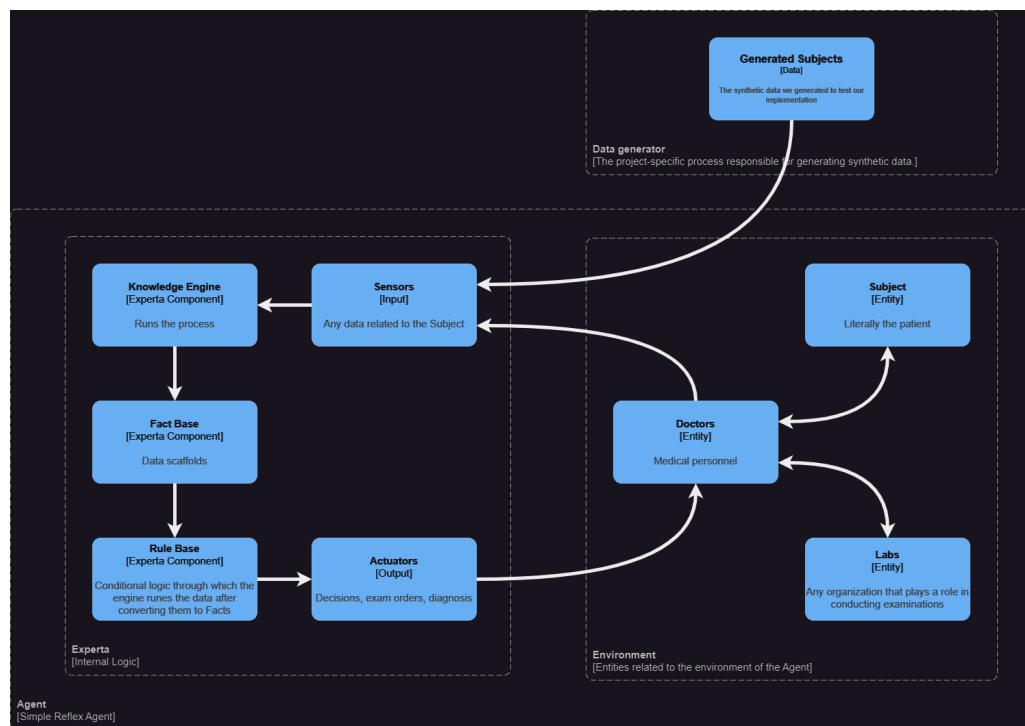


Figure 3.4: Agent's Components

Internal Logic

In the “Internal Logic” part of our Expert System one will find the *Expert* library. *Expert* is a rule based system designed to build expert systems with conditional logic (if-then rules). Like all other expert systems, it works by using a set of rules to analyze the provided inputs and deliver an output. The primary components of *Expert* are the Fact base and the Rule base which work as the memory and the knowledge engine of the Agent respectively. The fact base holds data describing a condition that will be used in a Rule. The Rule base is a set of rules, each of which has a condition and an action. A Fact is literally a scaffold describing some data. In other words, we could say that a Fact is a custom data type which *Expert* fills with the actual data of each sample and runs it through the Rule base. When the condition of a Rule is met by the facts, the Rule “fires”, and the system carries out the action. This could involve simply returning a value, setting a variable, calling another function, or anything else the system is designed to do.

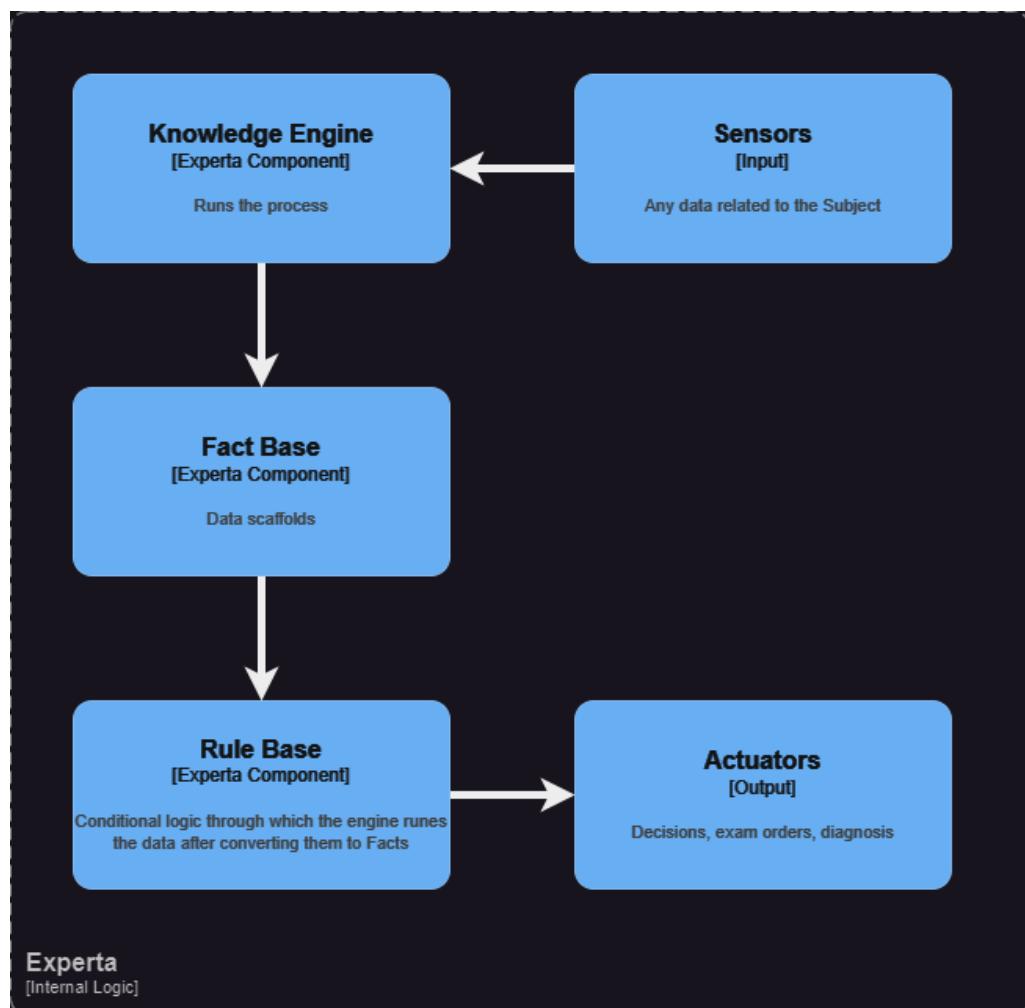


Figure 3.5: Agent’s Internal Logic

Environment

The environment of the Agent is composed of all the entities related to the Doctors, the Labs, the Subjects and any other information external to the Agent. The interface of Agent to communicate with these entities are the Sensors and Actuators, or in other words, the

Input and Output of the Expert System, where the Sensors could be anything from a Subject answering a questioner, to a Doctor filling a web form with the Subject symptoms or providing the results of an imaging examination to an Agent with image classification capabilities. The Sensors are all the actions that the Expert System could provide to the human expert as support to take a decision, make a diagnosis or order additional examinations.

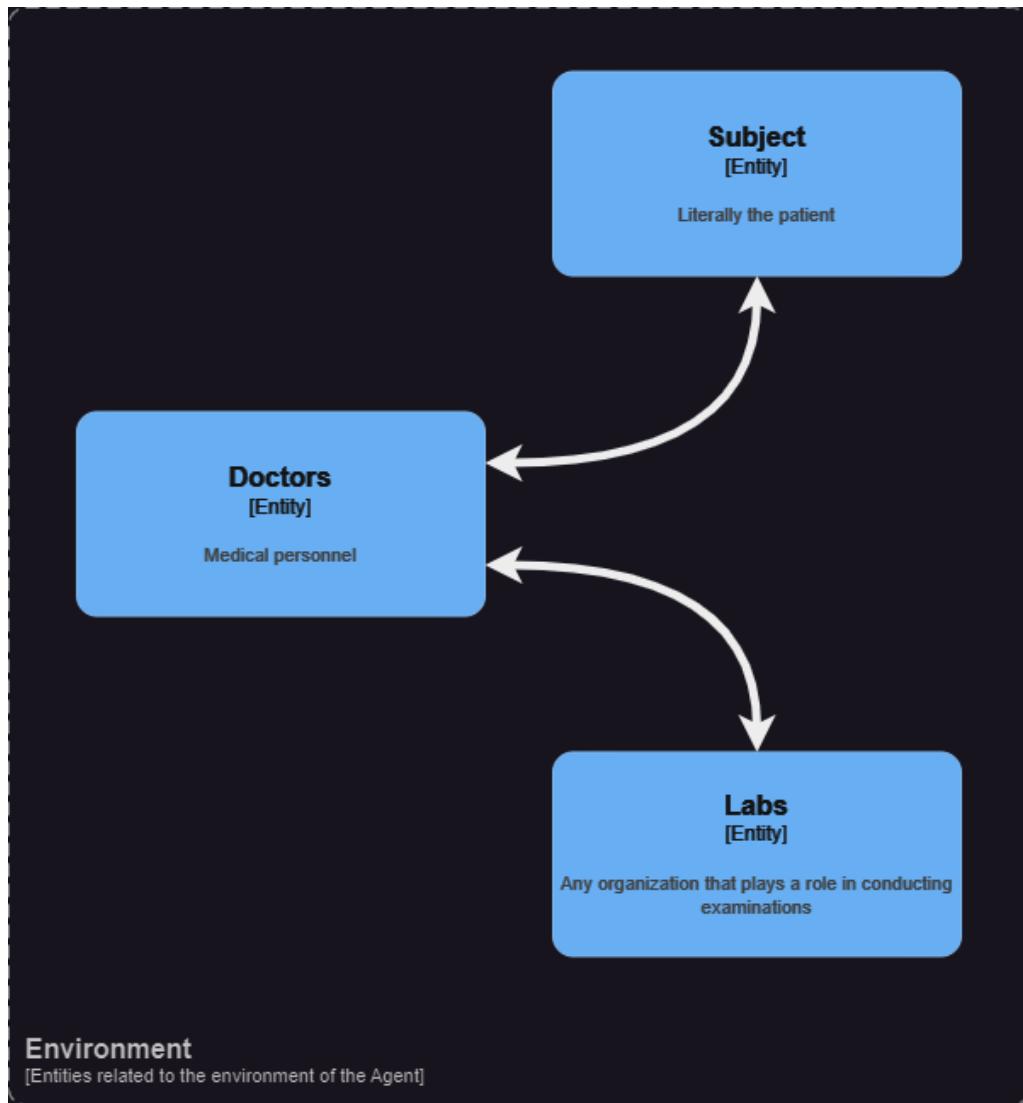


Figure 3.6: Agent's Environment.

Synthetic data

Regarding the generation of synthetic data, this task included some challenges that were not clear right from the beginning of the implementation design. After having created the class that represents the Subject it's easy to instantiate many Subjects, however initializing the individual properties of each Subject requires domain knowledge.

The difficult part of this process is to initialize the properties with values that are not conflicting regarding our context. For example, to elaborate further on this issue, we should avoid generating a Subject with such symptoms and exam results that would lead the TNM methodology to estimate a T1 stage for the primary tumor and a M1b stage for

metastasis, simply because there is no rule having conditions with such a combination of values. Therefore, if we did so, that would lead to a sample of our synthetic dataset triggering no rule and thus getting no estimate for that particular Subject, or even causing an error if we haven't foreseen this scenario to handle it with either some default rule or a try/catch pattern.

Therefore, since each time the system cannot estimate a T/N/M value, triggers a do_exams method that belongs in the Lab class, we handled this issue but using conditional statements that manually took care some of the conflicting scenarios. For example, we made sure that the diameter of Tumor would always be 0 if no mass has been detected during the X-rays exam. However, after many tries, the generator still created some Subjects with some properties combination that couldn't trigger any Rule. So, a second attempt was made with predefined properties, that the generator made use to create the Subject instances, thus solving this issue.

Implementation

To build our expert system, apart from the Rules and the Facts, we needed a Knowledge Engine that would use the Fact representation of our data to run them against the Rule Base and create Actions as support to the domain expert. In our implementation we initially experimented with the “PyKE” and “pyKnow” libraries, with which we found some technical problems and ultimately, we were led to use the “experta” library. Experta is currently the most popular Expert System Python library available, and it is actually a pyKnow fork with backwards compatibility. Which means that much of the Rule Base we wrote on the first stage of the project did not even need syntax adjustment to work property with the Experta library. The components of our Implementation consist of the following Python Classes and Jupyter Notebooks that were used for the execution of the experiments.

- **experiment.ipynb**
 - The main Jupyter notebook to run the experiments
- **generator.ipynb**
 - The Jupyter notebook from which the synthetic data are generated
- **testing.ipynb**
 - A Jupyter notebook that has some predefined cases to validate the Rule Base.
- **doctor.py**
 - All methods related to a doctor such as the estimate method.
- **lab.py**
 - Methods related to conducting exams, like the “exam_for_tumor” method.
- **subject.py**
 - The structure of the data we hold for each Subject.
- **generator.py**

- The actual methods responsible for generating synthetic data.
- **experta-wrapper.py**
 - The class where we hold the implementation of our Fact and Rule Bases and any project specific related methods.
- **logs-custom.txt and logs-experta.txt**
 - The files where we keep the logs of each experiment.

The estimate method is the entry point of our experiments, and it has three main stages. The first being the determining of whether a Subject is suspected of having cancer. The second is determining the Tumor, Lymph nodes condition and possible Metastasis using the TNM methodology. And the final step is using the TNM values to find the relevant stage using the Experta engine.

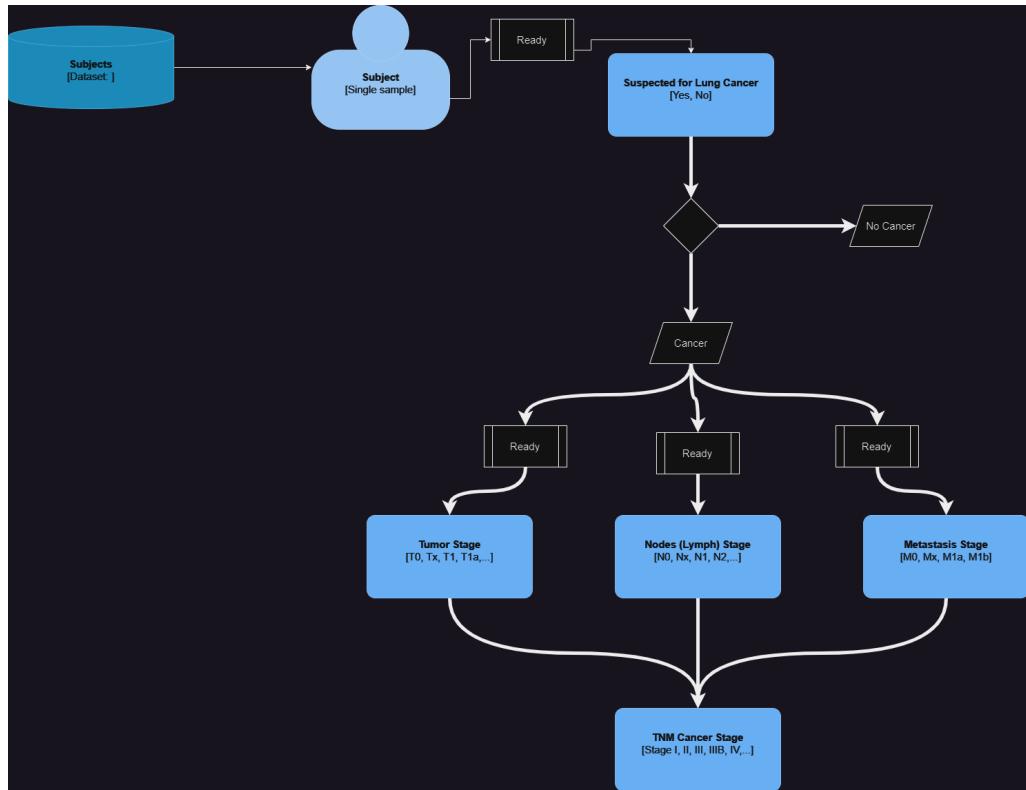


Figure 3.7: Estimate Function.

Estimation time and cost

Another important functionality of our implementation worth mentioning is the fact the whenever the Agent performs an additional exam for a Subject it also calculates and adds the financial cost and the delay of the exam suggested. The actual value of cost and delay is calculated from a function that gets the Min and Max cost and delay from two relevant look-up tables (Examination cost and time) and makes use of a Gaussian distribution function to return the estimated cost and delay of the exam that will be accumulated to the already existing values of the Subject.

	Cost		Time	
	Min	Max	Min	Max
X-rays	8.0	10.0	2	4
CT-Scan	40.0	75.0	7	45
Cytologic	15.0	20.0	3	4
Bronchoscopy	15.0	20.0	2	4
FNA	90.0	110.0	5	30
PET Scan	750.0	800.0	5	60
FNA and PET Scan	840.0	910.0	10	90
MRI	120.0	150.0	5	15
RO Bones	8.0	10.0	2	4
Scintigraphy	240.0	260.0	3	7

Figure 3.8: Examination cost and time.

Logging

Both for the explainability of the inference logic of the agent and for debugging purposes, we are recording two types of logs. First of all, we are making use of the built-in experts method “watch” which allows us to monitor both the rules and the facts. For example, when we are trying to determine whether a subject is susceptible to having cancer and the relevant symptoms are the following, we observe that a Rule is fired and correctly returned True, given that there is at least one symptom present and that indeed such a Rule exists.

```
INFO:experta.watchers.FACTS: ==> <f-1>: SUSPICION\_FACTS(smoking=False,
asbestos=False, radio=True, history=False, tsymptoms=True, nsymptoms=True,
msymptoms=True)
```

```
INFO:experta.watchers.RULES:FIRE 1 suspicion\_exists: <f-1>
```

```
INFO:experta.watchers.FACTS: ==> <f-2>: Result(value='True')
```

Therefore, the Experts library provides us with a way to monitor both which Fact values were tested against with the engine and which Rules ultimately fired and what was their value returned. Finally, we save both the Experts and our custom logs into text files, from which we could later retrieve that information for exploratory data analysis or other purposes.

Chapter 4

Conclusion

Using an expert system has many advantages, such as:

- **Accuracy:** ES is not susceptible to human error or emotional influence, so they can make decisions based on defined rules and facts.
- **Sensible deduction:** Expert systems use a variety of principles, such as if-then rules, to infer conclusions from information already known.
- **Stability:** When human experts retire, a lot of specialized knowledge could follow them. Knowledge-based systems offer an everlasting reservoir for information and knowledge.
- **Cost management:** Compared to the cost of hiring human specialists, expert systems are relatively cheap. They can assist in making judgments more quickly and inexpensively.

Although, expert systems have also disadvantages like the following:

- **Linear thought:** Expert systems are not truly capable of addressing problems. The ability to think nonlinearly and derive conclusions using auxiliary data is one of the benefits of human intelligence.
- **Lack of intuition and emotion:** People can use common sense and instinct to solve difficulties when they have intuition. Intuition is not a trait of machines. Human emotion can be helpful and important in some situations, such as making a medical diagnosis, for example. For instance, an expert system may lack the emotional intelligence necessary to provide sensitive medical information to a patient.

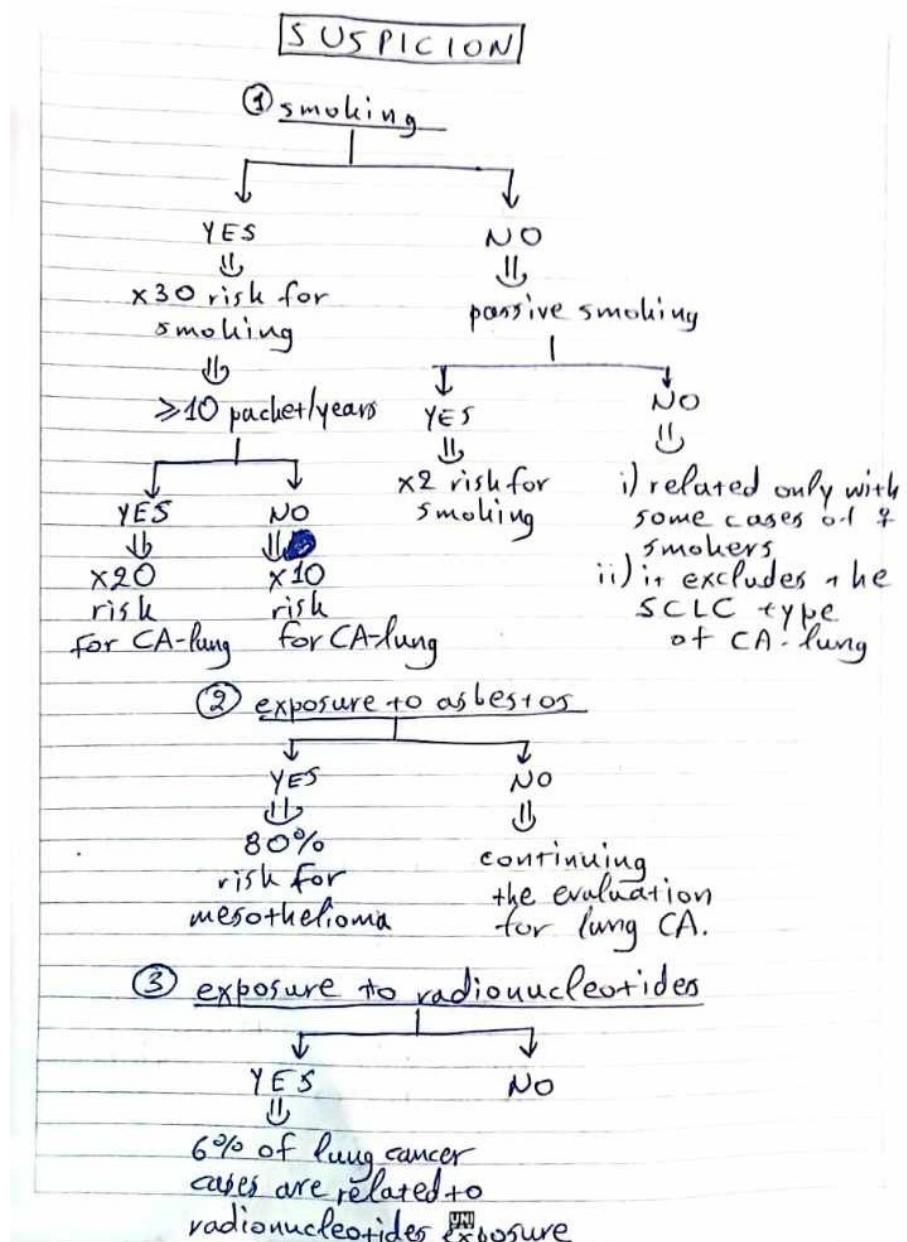
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Appendix A

Knowledge Base

A.0.1 Suspicion



④ history of CA - upper respiratory tract or GIT or head-neck cancer.

↳ cancerization effect.

↳ increases the risk for lung cancer.

⑤ possible symptoms by the primary tumor:

- i) chest pain $\Rightarrow 0,55$
- ii) haemoptysis $\Rightarrow 2,94$
- iii) cough $\Rightarrow 0,33$
- iv) dyspnea $\Rightarrow 0,4$
- v) hoarseness $\Rightarrow 0,26$

⑥ possible metastatic symptoms:

- i) bones pain
- ii) automatic fractures
- iii) intestinal contractions.

⑦ possible paraneoplastic symptoms:

- i) hypercalcemia
- ii) weight loss
- iii) ↑ PTH-related peptide
- iv) ↑ ACTH and Cushing syndrome

⑧ [physical examination]

① wheezing or ↓ decreased lung sounds

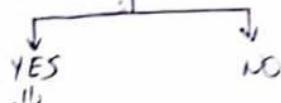
② Horner ~~symptoms~~ syndrome symptoms

- i) miosis
- ii) ptosis
- iii) anidrosis
- iv) enophthalmos
- v) loss of ciliospinal reflex



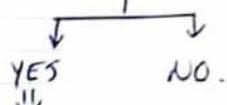
With risk for tumor on pulmonary apex. \Rightarrow Pancoast tumors

③ palpable, hard, painless ~~supra~~subcervical,
cervical lymph nodes



↓
it will require
(N)evaluation and
FNA in case of
TRUE for Tumor.

④ symptoms from the brachial plexus



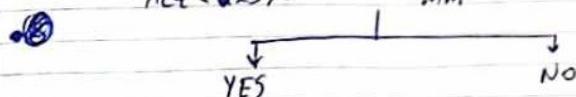
↓
Pancoast
tumor

⑤ hepatomegaly → YES ⇒ it will require
CT ~~abdominal~~
NO

⑥ skin nodules → YES ⇒ biopsy
NO.

LAB TESTS

① CBC ⇒ anemia, leukopenia, thrombopenia
Hb < 10 g/dl $< 4000 \text{/mm}^3$ $< 150000/\text{mm}^3$
Hct < 25%

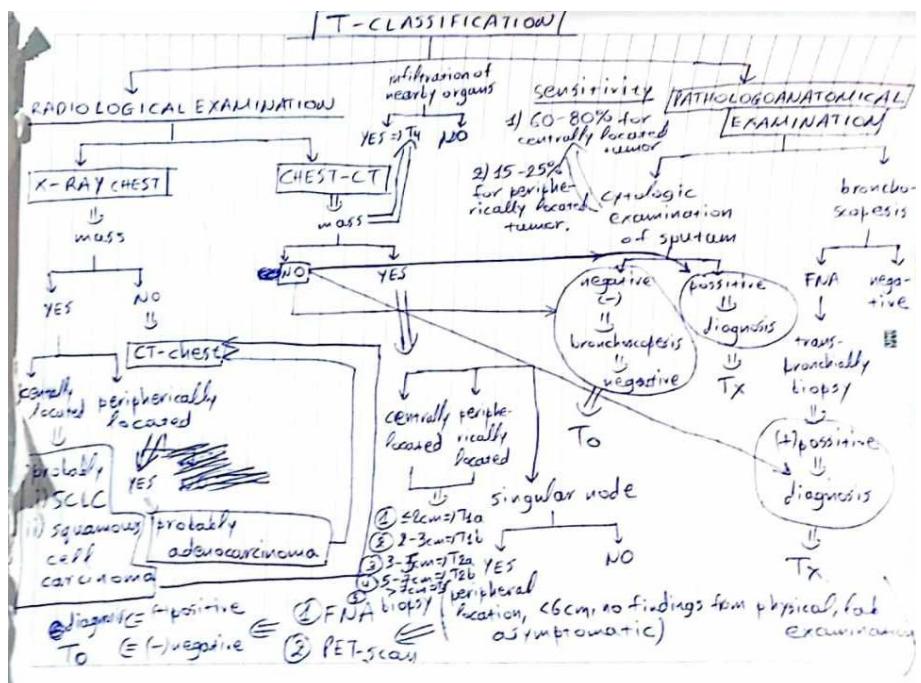


↓
possible infiltration
of bone marrow.

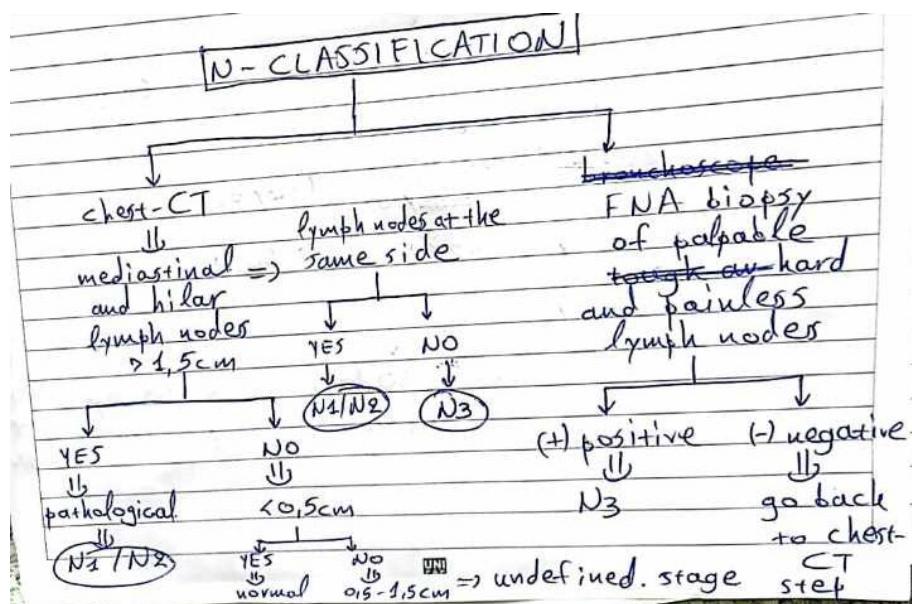
② liver tests ⇒ ↑ SGOT ↑ SGPT ↑ ALP ↑ γ-GT ↑ lactate
↓ albumin ⇒ YES = possible
liver metastases

- ③ ↑ ALP \Rightarrow also possible bone metastases
- ④ ↑ BUN and ↑ Cr \Rightarrow kidney injury.
- ⑤ $\frac{\uparrow \text{Ca}^{2+}}{\downarrow \text{PTH}}$ \Rightarrow possible paraneoplastic syndrome or bone metastases
- ⑥ ↑ K⁺ ↑ PO₄³⁻ ↑ uric acid \Rightarrow tumor lysis syndrome
- ⑦ ↑ LDH \Rightarrow bone marrow infiltration possibly
- ⑧ ↑ PT ↑ INR \Rightarrow possible liver metastases.

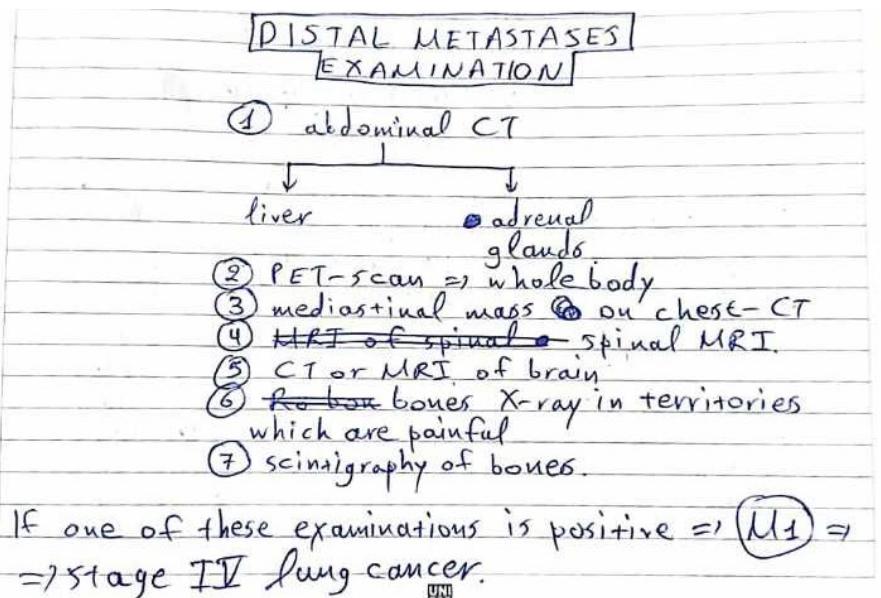
A.0.2 T Classification



A.0.3 N Classification



A.0.4 M Classification



Appendix B

Expert System

B.0.1 Facts

```
from experta import *

class Result(Fact):
    value = Field(str, default="")

class BaseStage(KnowledgeEngine):
    def get_result(self):
        for fact in self.facts.values():
            if isinstance(fact, Result):
                return fact["value"]
        return None

# Initialize the Facts

class SUSPICION_FACTS(Fact):
    smoking = Field(bool, mandatory=False)
    asbestos = Field(bool, mandatory=False)
    radio = Field(bool, mandatory=False)
    history = Field(bool, mandatory=False)
    tsymptoms = Field(bool, mandatory=False)
    nsymptoms = Field(bool, mandatory=False)
    msymptoms = Field(bool, mandatory=False)

class TUMOR_FACTS(Fact):
    mass = Field(bool, mandatory=True)
    diameter = Field(float, mandatory=False)
    bronchoscopy = Field(bool, mandatory=False)
    cytologic = Field(bool, mandatory=False)
    nearby_organs = Field(bool, mandatory=False)
    fna_and_pet_scan = Field(bool, mandatory=False)

class NODES_FACTS(Fact):
    lymph_nodes_size = Field(float, mandatory=True)
    peribronchial_metastasis = Field(bool, mandatory=False)
    mediastinal_metastasis = Field(bool, mandatory=False)
    fna_positive = Field(bool, mandatory=False)

class METASTASIS_FACTS(Fact):
    separate_tumor_nodules = Field(bool, mandatory=False)
    distant_metastasis = Field(bool, mandatory=False)

class TNM_FACTS(Fact):
    T = Field(str, mandatory=False)
    N = Field(str, mandatory=False)
    M = Field(str, mandatory=False)
```

B.0.2 Rules

Suspicion Model

```

class SuspicionInvestigation(BaseStage):
    @Rule(SUSPICION_FACTS(smoking=False, asbestos=False, radio=False, history=False, tsymptoms=False, nsymptoms=False, msymptoms=False))
    def suspicion_does_not_exist(self):
        self.declare(Result(value = 'False'))
    @Rule(OR(
        SUSPICION_FACTS(smoking=True, asbestos=W(), radio=W(), history=W(), tsymptoms=W(), nsymptoms=W(), msymptoms=W()),
        SUSPICION_FACTS(smoking=W(), asbestos=True, radio=W(), history=W(), tsymptoms=W(), nsymptoms=W(), msymptoms=W()),
        SUSPICION_FACTS(smoking=W(), asbestos=W(), radio=True, history=W(), tsymptoms=W(), nsymptoms=W(), msymptoms=W()),
        SUSPICION_FACTS(smoking=W(), asbestos=W(), radio=W(), history=True, tsymptoms=W(), nsymptoms=W(), msymptoms=W()),
        SUSPICION_FACTS(smoking=W(), asbestos=W(), radio=W(), history=W(), tsymptoms=True, nsymptoms=W(), msymptoms=W()),
        SUSPICION_FACTS(smoking=W(), asbestos=W(), radio=W(), history=W(), tsymptoms=W(), nsymptoms=True, msymptoms=W()),
        SUSPICION_FACTS(smoking=W(), asbestos=W(), radio=W(), history=W(), tsymptoms=W(), nsymptoms=W(), msymptoms=True)))
    def suspicion_exists(self):
        self.declare(Result(value = 'True'))

```

Tumor Model

```

class TumorStage(BaseStage):
    @Rule(TUMOR_FACTS(mass=False, diameter=P(lambda x: x==0.0),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=False, fna_and_pet_scan=False))
    def rule_tumor_t0(self):
        self.declare(Result(value='T0'))
    @Rule(OR(
        TUMOR_FACTS(mass=False, diameter=P(lambda x: x==0),
                     bronchoscopesis=False, cytologic=True, nearby_organisms=False, fna_and_pet_scan=False),
        TUMOR_FACTS(mass=False, diameter=P(lambda x: x==0),
                     bronchoscopesis=True, cytologic=False, nearby_organisms=False, fna_and_pet_scan=False)))
    def rule_tumor_tx(self):
        self.declare(Result(value='Tx'))
    @Rule(TUMOR_FACTS(mass=True, diameter=P(lambda x: x <= 2),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=False, fna_and_pet_scan=True))
    def rule_tumor_t1a(self):
        self.declare(Result(value='T1a'))
    @Rule(TUMOR_FACTS(mass=True, diameter=P(lambda x: 2 < x <= 3),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=False, fna_and_pet_scan=True))
    def rule_tumor_t1b(self):
        self.declare(Result(value='T1b'))
    @Rule(TUMOR_FACTS(mass=True, diameter=P(lambda x: 3 < x <= 5),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=False, fna_and_pet_scan=True))
    def rule_tumor_t2a(self):
        self.declare(Result(value='T2a'))
    @Rule(TUMOR_FACTS(mass=True, diameter=P(lambda x: 5 < x <= 7),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=False, fna_and_pet_scan=True))
    def rule_tumor_t2b(self):
        self.declare(Result(value='T2b'))
    @Rule(TUMOR_FACTS(mass=True, diameter=P(lambda x: x > 7),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=False, fna_and_pet_scan=W()))
    def rule_tumor_t3(self):
        self.declare(Result(value='T3'))
    @Rule(TUMOR_FACTS(mass=True, diameter=W(),
                      bronchoscopesis=W(), cytologic=W(), nearby_organisms=True, fna_and_pet_scan=W()))
    def rule_tumor_t4(self):
        self.declare(Result(value='T4'))

```

Nodes Model

```
class NodesStage(BaseStage):
    @Rule(NODES_FACTS(lymph_nodes_size=P(lambda x: x < 0.5),
                      peribronchial_metastasis=False, mediastinal_metastasis=False, fna_positive=False))
    def rule_nodes_stage_n0(self):
        self.declare(Result(value='N0'))
    @Rule(NODES_FACTS(lymph_nodes_size=P(lambda x: 0.5 <= x <= 1.5),
                      peribronchial_metastasis=False, mediastinal_metastasis=False, fna_positive=False))
    def rule_nodes_stage_nx(self):
        self.declare(Result(value='Nx'))
    @Rule(NODES_FACTS(lymph_nodes_size=P(lambda x: x > 1.5),
                      peribronchial_metastasis=True, mediastinal_metastasis=False, fna_positive=False))
    def rule_nodes_stage_n1(self):
        self.declare(Result(value='N1'))
    @Rule(NODES_FACTS(lymph_nodes_size=P(lambda x: x > 1.5),
                      peribronchial_metastasis=W(), mediastinal_metastasis=True, fna_positive=False))
    def rule_nodes_stage_n2(self):
        self.declare(Result(value='N2'))
    @Rule(NODES_FACTS(lymph_nodes_size=W(),
                      peribronchial_metastasis=W(), mediastinal_metastasis=W(), fna_positive=True))
    def rule_nodes_stage_n3(self):
        self.declare(Result(value='N3'))
```

Metastasis Model

```
class MetastasisStage(BaseStage):
    @Rule(METASTASIS_FACTS(separate_tumor_nodules=False, distant_metastasis=False))
    def rule_metastasis_stage_m0(self):
        self.declare(Result(value='M0'))
    @Rule(METASTASIS_FACTS(separate_tumor_nodules=True, distant_metastasis=False))
    def rule_metastasis_stage_m1a(self):
        self.declare(Result(value='M1a'))
    @Rule(METASTASIS_FACTS(separate_tumor_nodules=W(), distant_metastasis=True))
    def rule_metastasis_stage_m1b(self):
        self.declare(Result(value='M2b'))
```

Cancer Stage Model

```

class CancerStage(BaseStage):
    @Rule(OR(TNM_FACTS(T='Tx', N=W(), M=W()),
             TNM_FACTS(T=W(), N='Nx', M=W()),
             TNM_FACTS(T=W(), N=W(), M='Mx')))
    def rule_stage_x(self):
        self.declare(Result(value='Stage Undetermined'))
    @Rule(TNM_FACTS(T='T0', N='N0', M='M0'))
    def rule_stage_0(self):
        self.declare(Result(value='No indication')) # No indication of Lung Cancer was found
    @Rule(TNM_FACTS(T='T1a', N='N0', M='M0'))
    def rule_stage_ia2(self):
        self.declare(Result(value="Stage IA2"))
    @Rule(TNM_FACTS(T='T1b', N='N0', M='M0'))
    def rule_stage_ia3(self):
        self.declare(Result(value="Stage IA3"))
    @Rule(OR(TNM_FACTS(T='T1c', N='N0', M='M0'),
             TNM_FACTS(T='T2a', N='N0', M='M0')))
    def rule_stage_ib(self):
        self.declare(Result(value="Stage IB"))
    @Rule(OR(TNM_FACTS(T='T2b', N='N0', M='M0'),
             TNM_FACTS(T='T3', N='N0', M='M0')))
    def rule_stage_iia(self):
        self.declare(Result(value="Stage IIA"))
    @Rule(OR(TNM_FACTS(T='T1', N='N1', M='M0'),
             TNM_FACTS(T='T2', N='N1', M='M0')))
    def rule_stage_iib(self):
        self.declare(Result(value="Stage IIB"))
    @Rule(OR(TNM_FACTS(T='T1', N='N2', M='M0'),
             TNM_FACTS(T='T2', N='N2', M='M0'),
             TNM_FACTS(T='T3', N='N1', M='M0'),
             TNM_FACTS(T='T3', N='N2', M='M0'),
             TNM_FACTS(T='T4', N='N1', M='M0'),
             TNM_FACTS(T='T4', N='N2', M='M0')))
    def rule_stage_iiia(self):
        self.declare(Result(value="Stage IIIA"))
    @Rule(TNM_FACTS(T=W(), N='N3', M='M0'))
    def rule_stage_iiib(self):
        self.declare(Result(value="Stage IIIB"))
    @Rule(TNM_FACTS(T=W(), N=W(), M='M1a'))
    def rule_stage_iiic(self):
        self.declare(Result(value="Stage IIIC"))
    @Rule(OR(TNM_FACTS(T=W(), N=W(), M='M1b'),
             TNM_FACTS(T=W(), N=W(), M='M1c')))
    def rule_stage_iv(self):
        self.declare(Result(value="Stage IV"))

```

Appendix C

GitHub

[GitHub Repository URL](#)