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Model-based prediction of oncotherapy risks and side effects in bladder cancer

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Abstract

The prediction of cancer treatment side-effects requires the capturing of complex biophysical therapy parameters and the integration of different medical knowledge elements. In relation with radiotherapy, it is widely observed that the uncontrolled processes or undefined radiation therapy dose can decline the state of treatment. Precisely, the inability to manage the flow of available information, usually provided in heterogeneous formats, made it complicated to oversee and predict risks and effects of a prescribed treatment protocol. We think that, the optimization of knowledge representation and modelling in the context of evidence-based medicine can support the automated prediction of risks and side effects in oncotherapy. The following manuscript describes our methodology used for the design of a bladder cancer treatment side effects ontology embedded with evidence-based semantic rules and queries. Treatment knowledge is represented along with a particular consideration to the modelling of its referred risks and side effects. Our ontology model helps in improving the streamlining of medical practices and clinical decision-making. Within our semantic web approach, better strategies are applied for treatment selection with reference to possible side effects. Our ontology depicts real world scenario of developing treatment-related side effects. Furthermore, it is a clinical decision support system founding tool that highlights treatments efficiency. Our model shares treatment knowledge, facts and effects. Moreover, it includes medical evidence and incorporates a semantic rule base for systemic prediction results.

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1. Introduction

The considerable rise in the volume of medical information has radically transformed the medical thought and practice by making it overwhelming. More importantly, bladder cancer knowledge and treatment preferences are not static knowledge. They are rather driven by continuously emerging parameters. In addition, many recent studies [1] have revealed that onco-urology experts face more and more unanswered questions during practice and do not have sources of immediate knowledge. Nevertheless, unanswered questions remain a powerful motivation for developing an intelligent clinical decision support system, based on ontological knowledge representation.

The prediction of bladder cancer treatment adequacy involves vast amounts of events, activities, and actors. The involved complexity can generate difficult situations to be analysed for process improvement. Moreover, producing a semantic or logic-oriented representation of a knowledge base, in which the meaning of medical concepts and the relationships between them are finely expressed, is a key challenge in the domain of bladder cancer treatment. This resource can be represented formally so that it can be unambiguously exploited by a computer system. We believe that ontologies can help in this matter because thanks to its potential contribution in solving knowledge representation problems in so many medical cases [2]. Hence, it helps in extending the research study to harmonize our heterogeneous medical evidence and information for clinical knowledge management and medical predictive thinking. So far, many medical ontologies have been adapted for cancer disease representation however, the state of bladder cancer treatment risk and side-effects knowledge is still in need for a specific representation and modelling approaches. The existing ontologies in oncology are mostly focusing on the main terminological classification of the domain diseases. Neither bladder cancer treatment nor oncotherapy risks and effects were designed as a convenient model for future prevention or prediction aspects. And often, this did not consider oncology details or complex cancer problems, like treatment optimization for instance. On the other hand, the current state of concerned ontologies has not yet achieved a consensual acceptance and maturity with the use of formal semantics and logics.

Equally, the search for evidence during healthcare provision is highly required by healthcare governance frameworks [3]. Particularly, Evidence Based Medicine (EBM) became a preferred approach for practitioners, since it promotes the rigorous, explicit and judicious use of the most relevant evidence currently in place when making decisions about the right healthcare procedure for the patient. The use of ontologies in this context helps clinicians to better comply with oncotherapy and dosimetry procedures while benefiting from a large knowledgebase of information and evidences shared by the scientific community in the same domain.

In this paper, we use artificial intelligence technologies, especially ontology-based decision support techniques in order to meet the required level of specification and deal with our main problematics. This involves the use of a computer system that facilitates the task of reasoning while helping with decision-making. As part of the development of our medical information solution, we developed a medical ontology about the domain of bladder cancer. It specifies knowledge about medical acts, treatments, risks and side effects. This is to allow the prediction of consequences to the patient in oncotherapy while relying on medical and clinical evidences and proof. This ontology is the core of our EBM approach, incorporating artificial intelligence and medical reasoning in oncotherapy for bladder cancer treatment.

In the following sections, we discuss the context of our work and methods applied within our approach. An overview of the main related works to our research is mentioned in this paper Then we illustrate our approach and present the editing design methodology of our ontology. In the third section, we detail results about the structure of our ontology with its implementation facts. Also, we expose the features of our ontology model and the evaluations of treatments side effects rules. Then, we discuss our results in section four. Finally, we conclude the content of this paper and finish with some prospects and future work.

2. Related work

Recently, many studies about ontologies and semantic web representation have been established in medicine, but very few works concerned bladder cancer. Among them, three main categories of research work focused on medical decision support reasoning, which were: ontologies, information systems and databases. We found that general ontologies were trying to cover the whole parts of biomedical domains, namely SNOMED [4], UMLS [5], or NCIT [6]. However, they were structurally not ready to deal with the needs of bladder cancer oncotherapy reasoning. Medical ontologies could be connected to core ontologies and cover, at least, a part of medical semiotics as FMA and CCAM. Pitie-Salpetriere Medical Oncology Service carried out a research about a decision support system dedicated to the dissemination and use of good practice guidelines in oncology combined with the Oncolor workflow model to develop ONCODOC system [7]. Another attempt was made by Edward H. et al, to build decision support system based on ontology and a rule base, specifically dedicated to oncology called ONCOCIN [8]. Indeed, it is found that making the difference between Hierarchy categories description and some relationships is ambiguous in SNOMED which poses problems in multiple inheritances. In a previous study Lossio-Ventura et al created a natural language processing (NLP)-based system which was limited by the performance this process method. This was to build an ontology about cancer and obesity [9]. But, the use of one risk factor decreased its efficacity. Some of the mentioned approaches were extended with more specific taxonomies, but these works did not cover all the concepts needed in our ontology modelling.

3. Methods

3.1. Data collection and analysis

Harvesting data and information from different online knowledge sources was carried out systematically throughout this study. We used a web crawler "pubCrawler", in order to crawl and extract related data, knowledge and information about patients' samples mentioned in previous research. We queried some biomedical sources through our customized pub crawler. Our crawler searched medical libraries and archives of biomedical and sciences literature including its related journals and reviews for specified text-based queries. This provided information on a personalized web page whenever new articles appear in both PubMed and the US National Library of Medicine (NLM). Moreover, when new sequences were found in Science Direct or GenBank, we were alerted via emails showing instant notifications then delivering full results. the amount of received hits is proportional to information tracking results. Our gathered query results were compared to previously retrieved information hits. Only new items remained to be compiled into a web user-interface. Results were sorted into groups of our four defined queries. Under each query, details are sorted by items and dates of sources entries. Furthermore, neighbourhood searches were launched in other databases.

Our strategy identified 3777 publications through database searching. 81 additional publications were identified through other sources. The process of data collection and study selection contained the following steps: identification, selection, eligibility, and inclusion. The process resulted 93 records that concern our study. These included articles served as evidence and afforded cases to fit our study. The process excluded duplicate publications. Then, remaining publications were reviewed for eligibility including reports of bladder cancer treatments, clinical cases and side effects of prescribed therapy protocols. After qualitative review, we met our 93 cases that met the quantitative inclusion criteria. This is to be used in our ontology-based decisions about bladder cancer treatments' side effects prediction.

3.2. Ontology for the prediction of risks and effects of treatments

Clinical reasoning, when grounded with evidence has so far proven certain effectiveness in obtained clinical results. The wide adoption of the semantic web [10] in biomedical science has made ontologies part of many medical applications, especially in oncology. These ontologies are becoming larger and more complex since it is being developed by large and diverse communities of researchers. This approach could also be useful for the case of bladder cancer where the domain may involve hundreds of thousands of complex entities [11]. In the present study, we aim to design and develop an ontological model to represent our knowledge and then use it for the prediction of treatment risks to the patient. The use of ontologies in this context allows to define a common vocabulary for researchers who need to share information in a domain as complex as that of bladder cancer treatment. It includes machine-readable definitions of basic concepts in the field and relationships between them.

Our ontology development targets the provision of explicit formal specifications of domain terms and relationships between them. It helps to share a common understanding of the information structure between people or software agents (terminology). It enables the reuse of domain knowledge (reuse or integrate multiple existing ontologies describing parts of the extended domain). Furthermore, it analyses domain knowledge (formal analysis of terms) and infers knowledge. We can integrate a large number of medical evidences on which our reasoning could be based. Furthermore, it encapsulates the output of a reasoning or a new fact as an entry and a new reusable evidence for future reasoning.

Developing an ontology refers to defining a dataset and its structure for other programs to use. Problem-solving methods use ontologies and knowledge bases built from ontologies. An ontology can then be used as a basis for some applications (functions). Our ontology could be extended and linked to a decision support system for a complete evidence-based reasoning. Hence, we also produce in this work a set of semantic rules to be used for predictions and deductions. A semantic web rule language (SWRL) rule has a semantic meaning by expressing the relationship between an antecedent and a consequent. Our choice to use these rules lies in their powerful inference and deductive reasoning. For example, the treatment parameters, predictable risks and side-effects could be defined by predicates and each predicate is expressed within the SWRL rules responsible for drawing conclusions of when these events might happen. The validation and the execution of SWRL rules are carried out by means of the Pellet rule engine in its advanced mode [12]. This choice is long, but it provides a precise reasoning and optimal analysis. In the context of the Semantic Web a recommendation has defined standard languages that are based on description logics. The Web Ontology Language (OWL) is based on the Resource Description Framework (RDF) standard data model, specifying an extensible mark-up language (XML) syntax [13][14]. OWL is the most used and expressive standard on which, our ontological model and knowledge representation relies the most. It is characterized by formal semantics. It is also approved by the World Wide Web Consortium (W3C). It is interpreted and described by an incorporated terminology of concepts and domain properties. An ontology consists of a set of axioms that place constraints on sets of individuals called "classes" and the types of permitted relationships between them [15]. This enables the creation of classes and properties with appropriate instances in order to identify our evidence- based domain knowledge corpus and its operations.

A concept class is a set of objects or instances forming the represented domain. Classes are constructed from logical descriptions that constrain the membership conditions. A class can be a subclass of another (hierarchy), inheriting the characteristics (properties, and other instance values) of the parent class (super class). This corresponds to the logic subsumption and logic description of the concept symbolized by the inclusion symbol $\subseteq$. All classes are subclasses of "*Owl: Thing*" (root class). For example, bladder cancer *Treatment* could be a subclass of class *Owl: Thing*, while *Rugae* and *Trigone* are subclasses of bladder *Anatomy*.

A property, named a role, is a binary relationship/predicate that specifies the characteristics of a class. For example, *TURBT hasSideEffectSeverityGrade 2*: This example links the object class *TURBT* (transurethral resection) to the data value 4, indicating its complication severity grade, by the datatype property *hasSideEffectSeverityGrade* as a logical role of description. Properties can have logical capacities as transitive, symmetric, inverse and functional. They have domain and range definition. Data type Properties are relations between instances of classes and RDF literals or 'datatypes' XML schema. Object Properties are relationships between instances of two classes.

An instance, named individual, is a domain object that corresponds to a logical description with values of a class, in which there is detailed knowledge that we want to model. For example: (*Fat*, *MuscleSubmucosa*, *BladderLiningTransional Cells*) are instances of *BladderWallLayersAnatomy*.

This helped us to define and describe our concerned approach methodology about bladder cancer treatment knowledge representation and management as shown in Fig. 1. In our top-down approach we start by modelling concepts and relationships at a very generic level, after which these elements are refined.

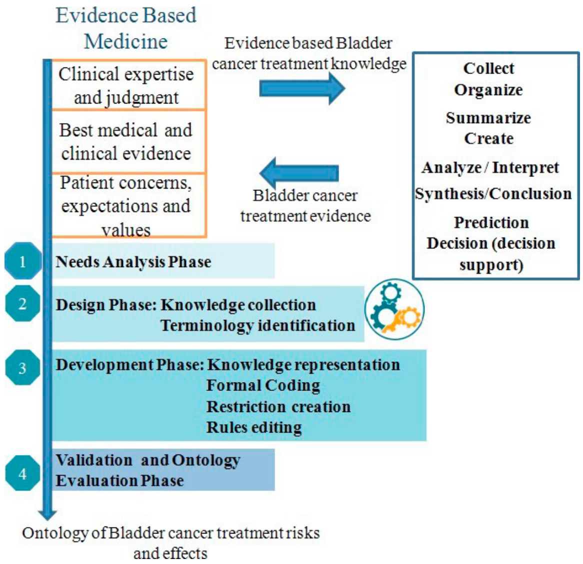

Fig. 1. The design methodology of Bladder cancer treatment risks and effects Ontology.

This approach is usually carried out manually and leads to a high-quality ontology. A high-level ontology can be reused and is generally used as a starting point for developing new ontologies [16]. Our main goal is to model the real-world context of Bladder cancer oncotherapy that could be achieved by the design of our ontology.

4. Results

In this section, we present the power of our ontological model when evaluating our restrictions and semantic rules. We take advantage of the efficiency and effectiveness which are considered two of the most powerful features in the semantic web technology [17]. Inference reasoning allows us to detect inconsistency and even undetectable degradations without semantics. To design and build our ontology we adopted an iterative and incremental cycle. This cycle is described as follows:

Firstly, the preliminary steps for the feasibility study and the requirements' specification. This allows us to clarify our requirements and development approach by asking questions about our objectives, constraints and the thematic framework of our ontology as well as identifying our core domain and its potential actors. Secondly, the design steps that include activities related to knowledge extraction, conceptualisation and terminology identification. This relates to the collection of information and knowledge related to bladder cancer treatment domain by medical evidences and information extracted from medical documents, scientific articles and standardised publications with clinicians' expertise. Terminology Identification is related to the representation of knowledge as abstract concepts, relationships and individuals in a natural language which traces the real medical world knowledge and evidence of bladder cancer treatment [18]. This is done thanks to the ability of OWL's terminological expressivity. Complex concepts are classified according to the content of their definition and hierarchy. Thirdly, the development phase includes formalization, evaluation and refinement. Here, formal and semantic modelling is directed to the relationships as properties between different concepts and instances. This is to build a model that will be the basis for ontological reasoning. We establish the relationship between concepts through object properties which were developed and formally encoded into classes (super classes and sub classes, properties, and instances). The creation of properties is accompanied by a specification of fields and ranges of these relationships between concepts and instances. To get a logic description of our complex concepts and relationships with specifications, we used Owl restrictions. The following example presents a formal specification of some classes and properties in our ontology:

$BCGIntravTherapy \sqsubseteq IntravesicalTherapy \sqcap hasComplication\ \forall\ (MildSE \sqcup ModerateSE \sqcup SevereSE \sqcup LifeThreateningSE \sqcup DeadlySE)\ \exists\ BladderMuscleSubmucosa$

Here, we define *BCGIntravTherapy* as a subclass of the *IntravesicalTherapy* concept which can have complication side effects: *MildSE* or *ModerateSE* or *SevereSE* or *LifeThreateningSE* or *DeadlySE,* applicable on a specific Anatomy concept which is the *BladderMuscleSubmucosa*.

At this level, after having all knowledge in a base, we have to write basic semantic evidence-based prediction rules in SWRL. Particularly these rules focus on the deduction of treatments risks and effects by referring to actual and current clinical evidence [19]. For example:

Chemotherapy(?X) ∧ hasStage(?X, ?S) ∧ swrlb:lessThan(?S, 1)→ compliance (?X, false): This means that if an x Chemotherapy procedure is given when the cancer has a stage under 1, it is considered as non-compliant. Otherwise, the procedure prescribed by the oncologist should turn to be compliant. These deductions represent a very important feature in the ontology. Then the rules are presented each of this form, with a prediction result as a reasoning conclusion. As a later step, we use SQWRL queries to get instant reasoning results and a selection of specific inadequate cases and possible complications as shown in the following example:

BCPatient (?P) ∧ hasStage (?P, ?S) ∧ swrlb:lessThan (?S, 1)∧ hasComplication (?P, ?C) ∧ hasTreatment (?P, TURBT) ∧ →sqwrl: select (?P, ?C): This aims to detect all BC complications at early staged patients (less than 1) associated with the couple (patient/treatment) combination while applying TURBT treatment. Results showed side effects (*Hematuria, Incontinence, BladderInfection, Pain*) associated to patient with non-muscle invasive Bladder cancer (*PNMIBC008*). Finally, the operational step of our approach is to validate, implement, manipulate and maintain the ontology. The evaluation of the ontology is a crucial phase. It can be done in different ways, either by proposing a set of metrics, or by comparing the prescribed treatment offered by the clinician to medical knowledge standards, as shown in the previous example. Indeed, this phase includes three parallel stages namely the comparison of the concepts, the comparison of the relations and the comparison of the instances of the concepts. This step requires the intervention of the domain expert. The validation is in terms of consistency, taxonomy, inference and completeness.

4.1. Knowledge representation and reasoning

To get an ontology-based clinical reasoning about risks and effects of bladder cancer treatment, some special phases included in our methodology are explained as follows. The initial phase of knowledge representation activates the elaboration and knowledge organization. Description and specification of classes are set using restrictions. A model of concepts is obtained at the end of this representation, allowing us to generate relevant analysis hypotheses and probable assumptions of risks and oncological effects. Facts interpretation and the evaluation of the hypotheses serve to get additional information which, consequently, modifies the initial representation until a knowledge model is obtained. This allows an optimal prediction at the end of a bladder cancer treatment. With this ontology the explicit use of formal medical knowledge in the process of clinical reasoning diminishes with the contribution of expertise and the addition of clinical evidence which in their turn become logical and practical knowledge. This enriches our ontology and help to continuously improve it. The obtained knowledge forms the basis of our reasoning about facts in the context of risk and effect prediction at the end of a certain bladder cancer treatment process. With the clinical activity, new information is integrated into our knowledge model, which makes this evidence applicable in the given medical context.

Nevertheless, the ontology knowledge is still present in our decision support system. It is used 1) to place the constraints on the acceptable values of OWL axioms; 2) to alert the clinician when a discovery does not match what was expected; and 3) explicitly in situations where semantic rules need more specifications to generate hypotheses. The obtained operational scheme describes the medical competencies associating formal medical knowledge and the experience-based knowledge represented in our ontology through the use of significant roles, axioms and relationships. A Reasoning based on incorrect or inappropriate knowledge cannot be optimal. Therefore, the validation and the validity of the sources is an essential condition, although it is not the only guarantee for an adequate clinical reasoning. Our consistent domain knowledge is extracted from scientific articles on bladder cancer with its different treatments, possible risks and most likely effects. The composition of clinical questions in a clear and precise way is a main task which concerns diagnosis, etiology, treatment and the prognosis. Looking for relevant information in the literature and bibliographic databases enhanced our classification capabilities. Then, we moved to the evaluation of information validity and classify our evidence into individual studies (low level) or synthesis studies (high level). The goal is to improve the consistency and the quality of used evidence for a better management of patient's treatment predictions. The most important thing is not to practice evidence-based medicine on its own right, but to know in advance and in practice how far one's actions are supported by science, or even contradicts the evidence. Hence, it is complementary to see the outcome of practices on patients through medical expertise and consultation of real practiced examples on bladder cancer patients.

We used Protégé for the creation of OWL classes based on our ontological model [20]. It is a software ensuring the editing of ontologies. Thus, we added SWRL rules to be conducted with the Pellet inference engine [21]. These rules were used for the detection of inconsistency in the: bladder cancer treatment, the triggering of risks and side effects predictions as well as necessary actions to deal with the problem. These actions were performed automatically through customized SWRL specification through the use of concepts from our ontology. Our evidence-based queries were launched to ensure the detection and tracking of subjects with possible mismatches. In case of inconsistent treatment, risks or negative effects, remedial actions will be triggered to deal with the consequences. At the end of this, the result ensures the classification of the current treatment as incoherent while adding it as a new practical evidence to the ontology as well as its effects. On the other hand, the result ensures decision-making reliability to the clinician and beneficial to the patient.

5. Discussion

Our ontology describes the different concepts and properties needed for representing our bladder cancer knowledge within semantics and description logic. The root of this model is the *Owl:Thing* concept which is the set of all individuals. It represents the concept of understandings that we can instantiate from our model. This concept, as shown in Fig. 2., is related to the following concepts: *Person*, *TumourCancer*, *Treatment*, *RiskEffect*, *Anatomy*.

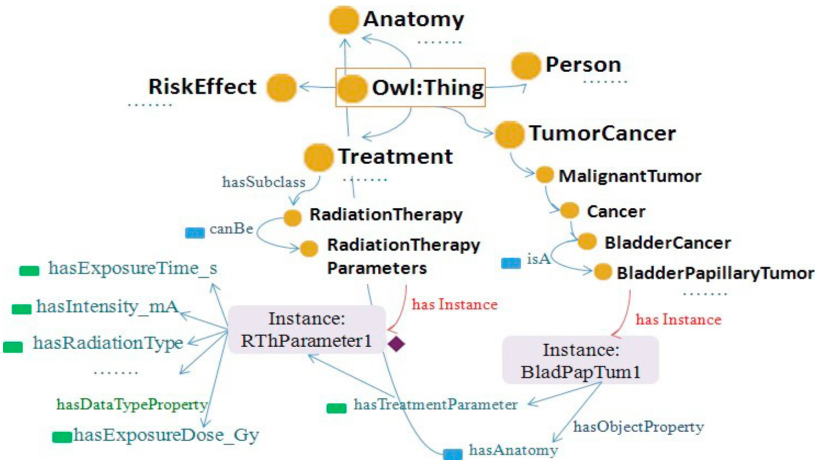

Fig. 2. An example of Hierarchical classification and relationships between classes and instances using properties.

The first concept defines main actors (people) involved in the treatment of bladder cancer, namely the staff of the medical team (clinicians or technicians) and patients. The second concept defines the context of bladder cancer, knowing that it is defined as a cancer under *MalignantTumour* subclass of *TumourCancer* class, while identifying its types, phases, pathological and biophysical characteristics. This class also ensures the binding of bladder cancer to other tumours (benign or malignant) that can be considered as secondary metastases and *OtherPathologies* that may be a cause or a consequence of our cancer. The third concept describes possible treatments related to bladder cancer. In this class, we instantiated our medical evidence and described protocols of necessary treatments. Thus, this class models the type and the nature of a bladder cancer treatment (drugs, treatment program and therapeutic process of bladder cancer), whether it is a biochemical or a radiation-based treatment. In addition, this class includes a subclass of risk supporting, which makes it possible to respond the prediction decision expected by our approach. This class is closely related to the results of our semantic prediction rules and therefore to the following *RiskEffect* class. The fourth class consists of all possible risks (long-term or short-term risks) and effects (negative or positive effects) resulting from some treatment. This class includes knowledge derived from medical evidence and used in our semantic reasoning as a reference and a result of inference. In addition, risks and effects are always related to the treatment class in our case. These last two concepts are the main super classes of our ontological model. They are linked, complementary and in a direct relationship.

Anatomy is another class that is found to be very important in this process. This class provides the taxonomy and categories needed to indicate the specific anatomical parts affected by the studied cancer and this helps to precise which parts of the body are at risk after a bladder cancer treatment. We have defined the set of concepts of ontology and the terms of the domain (the synonyms), as well as for the semantic relations connecting them. The resulting ontology has been structured into OWL language, which meets our needs in terms of expressiveness and manageability. We were able to identify 852 concepts, 1825 instances with actual objects of knowledge, 256 relationships and roles divided to 80 object-properties and 176 data-type-properties and 620 different treatment and predictive risk/effect rules. The set of concepts and terms has been reviewed by an oncology doctor and two nursing staff of the Oncology Department of a University Hospital. Furthermore, our ontology is validated in terms of consistency, taxonomy, inference and completeness [22]. The development of a bladder cancer treatment with risk and effect prediction ontology made it a special and a specific semantic approach. This, models and represents knowledge, based on medical evidence with a reasoning about treatment prediction.

6. Conclusion

In this article, we described a methodology to design and develop an ontology-based model to improve knowledge representation of bladder cancer treatments in order to allow the prediction of their underpinned risks and side effects. This could be considered as a proactive approach to patient's safety optimization when prescribing cancer treatment. By exploiting the semantic richness of ontology in the way of representing our concerned concepts, we have been able to develop a comprehensible and readable model for both the machine and the different actors involved in the bladder cancer treatment selection process. Thus, the reasoning techniques and the power of the inference rules presented in the ontology allow us to predict treatments' effectiveness and determine risks and effects in addition to the necessary preventive solutions. This also makes it possible to classify the currently prescribed treatments and patient experience as evidence to be used for future deductive reasoning. The feasibility of our model is evaluated using SWRL rules. Currently, we are planning to implement our ontological approach in a clinical decision support system in order to increase the efficiency and generalisability rate affecting the practice and treatment process of bladder cancer. Furthermore, the optimization of our ontological model helps with the profit maximization and meeting the expectations of clinicians and patients.

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