Modeling of Clinical Practice Guidelines for an Interactive Decision Support Using Ontologies

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Abstract— *Modern medicine typically offers a diverse set of treatment options, rapidly evolving over time. In this context, Clinical Practice Guidelines (CPGs) are able to provide recommendations for actions and by that a frame of reference for medical experts during various treatment processes. To facilitate the implementation of these recommendations, we propose an interactive decision support system (DSS). For this reason, the CPGs of Chronic Myeloid Leukemia, Myelodysplastic Syndromes, Mantle Cell Lymphoma, and Multiple Myeloma are formalized using ontologies. The resulting models serve as an exemplary basis for a DSS, providing patient-specific as well as CPG compliant recommendations.*

Keywords: Clinical Practice Guidelines, Treatment, Interactive Assistance, Decision Support, Ontology

1. Introduction

Curse and blessing of modern medicine can be seen in the variety and number of treatment options rapidly changing over time. Furthermore, the steady growth of published findings makes it almost impossible for an individual to keep their knowledge up-to-date [1]. Clinical Practice Guidelines (CPGs) can help to condense knowledge into recommendations for actions. Thereby, CPGs rely on consolidated medical knowledge for providing state-of-the-art care [2].

Although, this should bring scientific findings into practice, the use of CPGs at the point of treatment still represents a challenge. That is, because there is a gap between theoretical knowledge on the one side – which is typically given by lengthy documents written in prose [2] – and practical as well as patient-specific treatment solutions on the other side [3], [4], [5]. As a consequence, a passive dissemination of CPGs (e.g. by print media) has proven to have only little effect on the actual practitioners behavior [2], [6].

Therefore, we propose an interactive decision support facilitating the treatment process by bridging the gap between CPG recommendations and the actual treatment delivered to patients. Following this idea, in this contribution we elaborate an exemplary formalization of CPGs concerning Chronic Myeloid Leukemia (CML), Myelodysplastic Syndromes (MDS), Mantle Cell Lymphoma (MCL) and Multiple Myeloma (MM) using Ontologies. Thereby, the following main requirements of a decision support system (DSS) based on these models have been determined with the help of medical experts. Firstly, performed examinations and treatment action have to be stored. Secondly, warnings have to be issued in case examinations are missing or, thirdly, if abnormal results are observed. Finally, suitable examinations and treatment actions have to be proposed by the DSS.

2. Related Work

How ontological formalization can be leveraged in context of medical applications is elaborated in [7], [8], [9]. Thereby, an ontology-based decision support system is presented that allows to assess the risk factors of diabetic patients and provide appropriate treatment suggestions [7]. In [8] an ontology for cancer therapy is used to discover possible problems of data consistency in electronic patient records. In [9], a disease-specific ontology for the treatment of colon cancer using information found in medical abstracts is developed.

In this work, we focus on ontologies to formalize knowledge embodied in CPGs of complex cancerous diseases. Therefore, CML [10], [11], MDS [12], [13], MCL [14], [15], and MM [16], [17] are exemplary modeled. The developed ontology is basis of an interactive decision support for medical practitioners, providing patient-tailored recommendations during treatment. The use of ontologies for this application example has many advantages. One of them is that ontologies can encapsulate CPGs as classes and relationships. That means, in contrast to, e.g. graphic modeling languages, they allow to represent and facilitate the semantics of knowledge using relations and axioms. Given this formalized knowledge base, conclusions can then be drawn automatically.

Moreover, the formal representation of this knowledge base can be expanded, adapted and reused at any time [7] which is especially important in the given context. E.g. in clinical trials, new drugs and treatment options are being tested or drug side-effects and drug interactions are under investigation.

This leads to a knowledge base that is continuously subject to change. While new knowledge can be incorporated by extending the existing ontology, changes in knowledge can also be dealt with efficiently. E.g. if clinical trials show that limits of drug doses must be changed, it is sufficient to adjust the ontology in one place (i.e. there is no need for redundant adjustments).

Due to their high level of semantic expressiveness, ontologies are a suitable tool for modeling complex knowledge representations [18]. Furthermore, their use as foundation of knowledge-based decision systems are widely adopted [19].

3. Basics and Terminology of Ontologies

An ontology consists of a set of concepts, i.e. the classes and relations of the universe of discourse, as well as formal axioms which limit the semantics and guarantee a correct application of these concepts [20]. There is also a lexical level to describe the meaning of the concepts in natural language terms. Formally, an ontology is a tuple [20]

$$T = (O, L) \ ,$$

whereby O is the structure of the ontology and L is the lexicon. The latter is a set of human-readable term definitions. The ontologies structure is given by

$$O = \{A, K\} \ ,$$

where A is set of axioms that limit the semantics and guarantee a correct application of the concepts. K is the set of concepts, i.e. the union of the set of classes and the set of relations:

$$K = C \cup R \ .$$

Thereby C is the set of classes which contains the instances of the universe of discourse

$$C = \{c_1, \ldots, c_n\} \ ,$$

and R is the set of relations between the classes of the universe of discourse [21], so that

$$R : C \times C \ .$$

These classes and their relations can also be represented by a graph

$$G = (V, E) \ ,$$

where the set of vertices V is given by the set of classes C and the set of edges E is given by the set of relations R.

4. Modeling Approach

For modeling the cancerous diseases CML, MDS, MCL and MM, the methodology elaborated in [22] has been utilized. The process comprises several steps starting with (e.g.) the assessment of requirements. Furthermore, building and evaluating the ontology, e.g. by checking the fulfillment of requirements, is necessary. Finally, establishing a suitable documentation is important since inadequate documentation has been identified as one of the main barriers for effective use of ontologies [22].

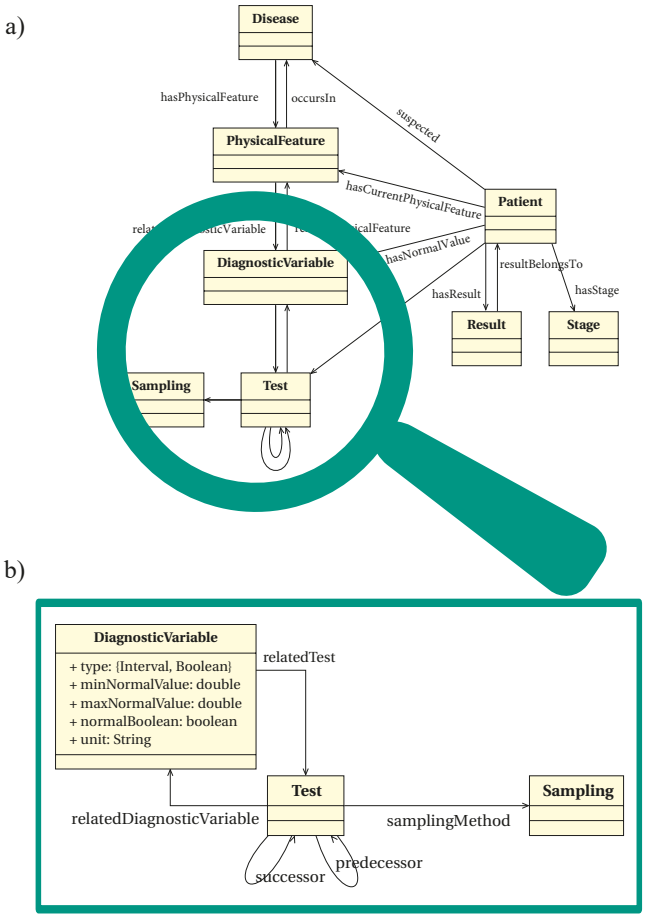

Fig. 1: Subfigure 1a) shows an overview of the classes and relations used for modeling test results. In Subfigure 1b), several classes and their relations are shown in more detail (magnifier). The class "DiagnosticVariable" incorporates, i.e., a reference range limited by "minNormValue" and "maxNormValue" (e.g. $[4 \cdot 10^9, 10 \cdot 10^9]$) as well as a unit (e.g. $1/L$). To model a sequence of tests, the functional relations "successor" and "predecessor" are used for class "Test". Furthermore, "Sampling" specifies how a test sample is obtained.

4.1 Examinations

During the treatment of cancerous diseases, examination values have to be collected continuously to check whether the treatment is effective or not. Subfigure 1a) gives an overview of the classes involved in the proposed modeling approach.

Thereby the class "Disease" contains information on the diagnosis as well as the treatment of the specific cancerous disease. A disease is characterized by a set of specific

physical features – e.g. leukopenia (lack of leukocytes). For this purpose, the class “PhysicalFeature” is created which is linked to a disease via the relation “hasPhysicalFeature”.

The class “DiagnosticVariable” depicted in Subfigure 1b) incorporates a reference range, a unit and a type for each component of a test. For instance, the reference range of leukocytes using the unit $1/L$ is given by $[4 \cdot 10^9, 10 \cdot 10^9]$. Therefore this variable is stored as type “Interval” using a “minNormalValue” of $4 \cdot 10^9$ and a “maxNormalValue” of $10 \cdot 10^9$ with “unit” $1/L$.

The class “Test” models different medical examinations like fine-needle aspiration biopsy or complete blood count (CBC). The latter has several related diagnostic variables such as hemoglobin or leukocytes. In order to represent this connection in the ontology, the class “Test” is connected to the class “DiagnosticVariable” via the relations “relatedTest” and “relatedDiagnosticVariable” – see Subfigure 1b).

To model a sequence of different tests, the functional relations called “successor” and “predecessor” are defined. Each test can also be assigned to one or more instances of the class “Sampling”. Thereby, class “Sampling” specifies how a test sample is obtained. E.g., a sample for hematopathological analysis of a tumor tissue can be obtained by fine needle biopsy or a more invasive incision biopsy.

To model the order of examinations, an axiom of the Semantic Web Rule Language is used:

$$\text{Patient}(?p) \wedge \text{suspected}(?p, \text{MCL}) \quad (1)$$

$$\rightarrow \text{hasTestSuggestion}(?p, \text{HistoryAndPhysicalMCL})\,. \quad (2)$$

In (1) it is checked if there is an instance of class “Patient” suspected of suffering from MCL[1]. If this is the case, the relation “hasTestSuggestion” is added to the ontology, whereby variable $?p$ is replaced by the corresponding instance (2). By doing this, history and physical examination is proposed initially. The class “Result”, cf. Subfigure 1a), is used to store patient specific examination values. These results are assigned to the patient via the relation “hasResult”.

Finally, in order to determine the progress of the disease, disease-specific axioms are defined. E.g., in case of MCL, a patient is assigned to stages “I” to “IV” via the relation "hasStage". The corresponding relation is shown in Subfigure 1a).

4.2 Treatment

Subfigure 2a) shows an overview of the classes and relations involved in the treatment of the diseases CML, MDS, MCL, and MM. Thereby, the central class is “Treatment”, from which subclasses can be formed, each representing a therapeutic option, cf. Subfigure 2b). There are three treatment approaches: radiation therapy, chemotherapy and treatment with drugs. Depending on the patient’s age and

[1]Please note: Variables in SWRL axioms are prefixed by a question mark.

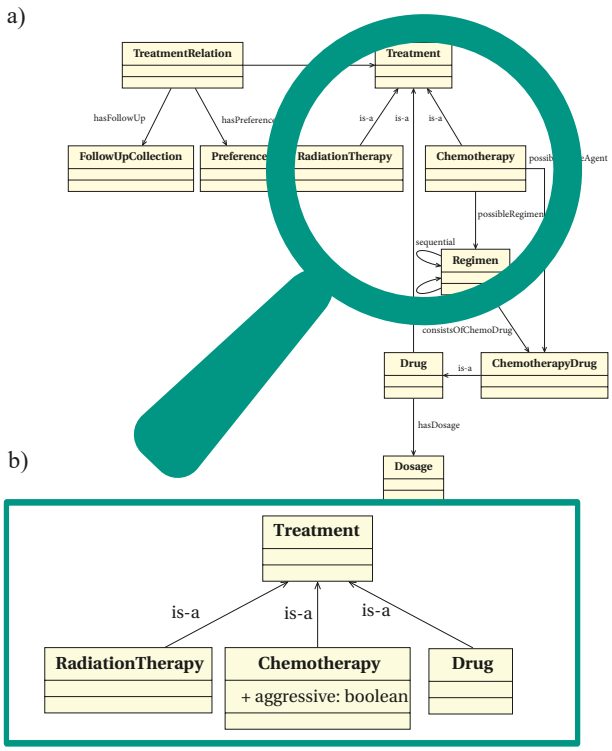

Fig. 2: Subfigure 2a) shows an overview of the classes and relations used for modeling the treatment. Subfigure 2b) depicts a detailed view of the class “Treatment” and its subclasses representing different treatment options. For simplification the classes “Surgery”, “TKI” and “BloodCellGrowthFactors” are not shown.

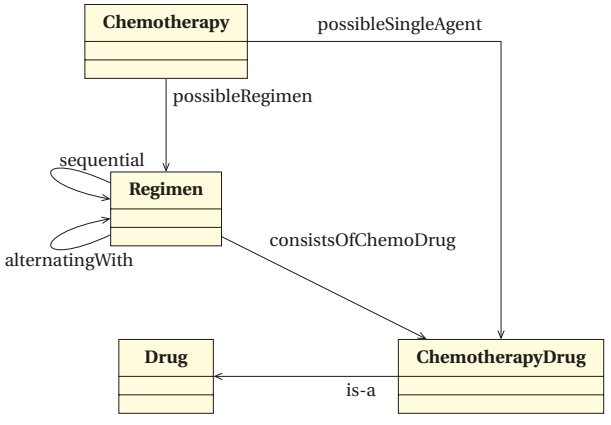

Fig. 3: Figure depicts the classes used for modeling a chemotherapy. Single chemotherapeutic drugs (single agents) or combinations of drugs can be used (regimens). The latter can be carried out sequentially or in alternation with other regimens.

preferences, chemotherapy can be carried out either low-intensity or high-intensity. This is represented by the boolean attribute aggressive of class “Chemotherapy” – iff the intensity of chemotherapy is high, this attribute is given the value “true”. To cover a wider range of diseases, further subclasses such as “Surgery”, “TKI” or “BloodCellGrowthFactors” are added. For simplification they are not depicted in Figure 2.

There are different types of chemotherapy drugs, acting in different ways to kill existing cancer cells or prevent the formation of new ones [15]. Often more than one drug is used – in this case the treatment is called a combination regimen (cf. Figure 3).

Otherwise, if exactly one drug is used, it is called a single agent. In order to map this assignment of chemotherapy to an associated medication, the relation “possibleSingleAgent” between the class “Chemotherapy” and “ChemotherapyDrug” is used. Thus, chemotherapies that consist only of one single drug can be represented.

If a chemotherapy consists of two or more medications, the class “Regimen” can be used. The relation “consistsOfChemoDrug” relates a combination regimen to any number of chemotherapy drugs. A combination regimen is assigned to chemotherapy via the relation “possibleRegimen”. Different combination regimes can be given alternately or sequentially (cf. e.g. MCL [14]). For their representation the relations “alternatingWith” and “sequential” for the class “Regimen” were created.

To facilitate extensions of the ontology regarding further details on chemotherapy cycles, four relations have been added to class “Drug” (cf. Figure 4). The first relation is “hasDosage” from class “Drug” to class “Dosage”. The latter contains the attributes “value” and “unit” for storing information about the dosage of a medication.

The second relation is given by “administrationDays” of the class Drug. It represents the fact that in a chemotherapy cycle, treatment days are followed by specific number of rest days (cf. e.g MCL [15]). To indicate the type of drug administration of a cancer treatment (i.e. subcutaneous, oral or intravenous), the third relation “administrationMethod” of class “Drug” is used. The frequency of drug administration can be specified using the fourth relation “administrationFrequency”. Possible values are QD or BID, whereby QD stands for “quaque die”, every day. BID stands for “bis in die”, twice a day. Further frequencies can be added to the range.

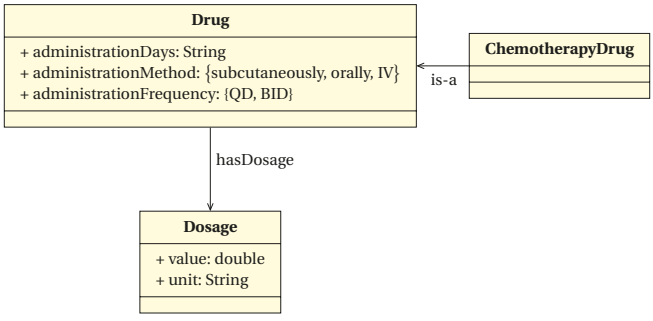

Fig. 4: Detailed view of the classes “Drug”, “Dosage” and subclass “ChemotherapyDrug”. The former incorporates several relations. Thereby, e.g., “administrationDays” represents the fact that a chemotherapy is typically carried out in cycles of treatment- and rest days. Furthermore, the frequency of drug administration (e.g BID, i.e. “twice a day”) is represented by “administrationFrequency”.

4.3 Multiple Treatment Options

To provide suitable treatment options, the class “Treatment” is not sufficient. That is because generally, a treatment may consist of several approaches. E.g for MCL in stage I or II, radiation therapy can be combined with chemotherapy. In addition, different treatment options can depend on the physical condition and preferences of a patient.

Moreover, for some treatments the CPG recommends tests to verify their efficacy. In order to implement these aspects a quinary relation is necessary to link a patient with two or more treatments and (depending on the treatment) a preference as well as a possibly large number of examinations. Therefore a design pattern is used [23]. Thereby, a n-ary relation is represented by a new class and n new relations. An instance of the relation that connects n individuals is an instance of this new class – e.g. the class “TreatmentRelation” is used to propose different treatment options for a patient (cf. Figure 5). The main treatment option is specified via the relation “mainTreatment”. E.g., for MCL in stage I or II, the main treatment is radiation therapy. If this treatment is combined with other approaches (e.g. chemotherapy), this information is added via the relation “inCombinationWith”.

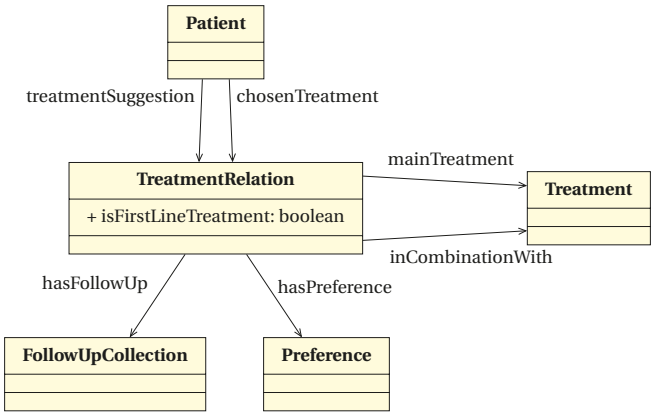

Fig. 5: Detailed view of the classes “TreatmentRelation”, “FollowUpCollection”, “Preference”, “Treatment”, and “Patient”. Thereby, e.g., “mainTreatment” specifies the primary treatment (e.g. radiation therapy) and combined approaches are specified by “in CombinationWith” (e.g. chemotherapy).

To be able to represent treatment preferences, the relation "hasPreference" is used. E.g. for MCL, depending on the stage, age and preference of the patient different treatment options can be chosen. This comprises, e.g. radiation therapy in combination with aggressive or less aggressive chemotherapy or radiation therapy without chemotherapy. Whereby a patient should be offered one of these three options, medical experts prefer specific treatments. E.g., radiation therapy without chemotherapy for MCL stage I patients or radiation therapy with less aggressive chemotherapy for older patients in stage II, and radiation therapy with aggressive chemotherapy for younger patients in Stage II. An instance of the class "TreatmentRelation" can be assigned to one of the instances "Preferred" and "Alternative" of class "Preference". This can be used to express whether medical experts prefer the current treatment for a patient or consider it as an alternative. In order to propose treatment options for a patient, the relation "treatmentSuggestion" is used. Which treatment options are actually proposed is determined by axioms. The medical expert can select one of the treatments by specifying the desired treatment option for the relation "chosenTreatment".

4.4 Follow-Up

Generally, CPGs recommend examinations to evaluate the treatment success. These so called follow-ups usually take place regularly over a longer period of time. E.g., after radiation therapy in combination with chemotherapy, complete blood counts are carried out every three months for a period of two years. However, the assignment of an examination to a regularly recurring period is not generally unique. E.g. for MM, every 3 to 6 months a complete blood count is carried out each year. To represent follow-up examinations, the design pattern for n-ary relations was used (cf. class $FollowUp$ in Figure 6). The scheduled examination is determined by the relation "requiredTest". The relation "followUpMapping" connects the class "FollowUp" to the class "Mapping".

The latter allows for capturing the time periods in which the specified examination has to be repeated. Using the relations "everyXMonths" and "years" of the class "Mapping", a typical statement such as "The examination is carried out every three months for two years" can be represented. In order to structure the information about the follow-up examinations, the class "FollowUpCollection" is used. Therby, the relation "consistsOfFollowUp" connects the classes "FollowUpCollection" with the class "FollowUp" in order to bundle the multitude of possible follow-up examinations. The class "FollowUpCollection" can be reached via the relation "hasFollowUp" of class "TreatmentRelation", because generally, different combinations of follow-up examinations are needed depending on the type of treatment.

After the follow-up examinations have been performed, results are stored in instances of class "Result" (cf. Section 4.1). The medical expert can then decide if the

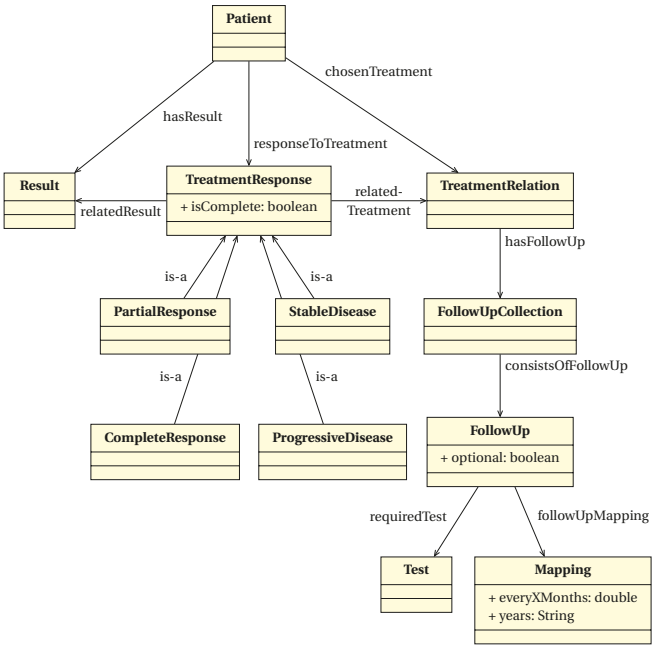

Fig. 6: Overview of the classes related to the treatment of a disease. The class "FollowUp" models an n-ary relation which is necessary to generally represent combinations of involved examinations. The class "FollowUpCollection" bundles these examinations.

treatment has been successful. The class "TreatmentResponse" contains the subclasses "CompleteResponse", "PartialResponse", "StableDisease", and "ProgressiveDisease". Therby, the physician determines which of these subclasses represent the patient's outcomes. Patients who have achieved complete remission will typically receive a special follow-up treatment. For this purpose, the relation "isComplete" is used, which is set to "true" by an axiom for instances of the class "CompleteResponse". Naturally, it is set to "false" for any instances of any other subclasses of "TreatmentResponse" – which facilitates the suggestion of subsequent treatments.

5. Verification

To verify the modeled ontologies for CML, MDS, MCL and MM, typical patients regarding cancer statistics are generated [24], [25]. These statistics document e.g. the number of newly diagnosed cancer diseases in Germany in 2012 as well as the mean age of onset. For the model implementation, the open-source ontology framwork Protégé [26] was used.

According to [24], 16,150 people were newly diagnosed with a non-Hodgkin's Lymphoma in Germany in 2012, which also includes MCL [14]. Among them are 8,580 men and 7,570 women. The average age of men being newly diagnosed with MCL is 70 years whereas the average age

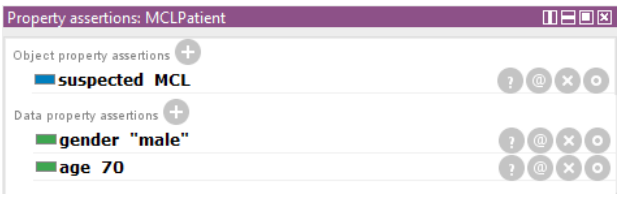

Fig. 7: Property assertions of a sampled MCL patient created on basis of cancer studies [24]. Screenshot of the Protégé ontology editor [26].

of newly diagnosed woman is 72 years. As a consequence, in a first step, a 70 year old male patient is sampled for verification (cf. Figure 7). To issue warnings if examinations are missing (cf. requirements in Section 1), corresponding tests to assess the missing values can be proposed by the DSS. To avoid inconsistencies by conflicting information at the same time, we do not model explicitly which values are missing but focus on the suggestion of tests in order to assess the corresponding values. Therefore, for the example patient, the diagnosis starts with a suggested test for the assessment of history and physical examination. This is represented by the object property assertion "hasTestSuggestion(MCLPatient, HistoryAndPhysicalMCL)", cf. Figure 8.

Please note, that the NCCN guidelines cite a variety of diagnostic tests, needed to confirm the suspicion of the disease under consideration. However, medical experts carry out tests in a patient-specific order – i.e. starting from non-invasive test to invasive tests. Therefore the DSS correctly proposes the non-invasive test of history and physical which includes e.g. the non-invasive palpation of the number of involved lymph nodes as well as the involvement of the spleen.

After carrying out the test, corresponding results are stored in the ontology (cf. requirement 1 in Section 1). For this, the ontology enables the creation of an instance of class "Result". For the sample patient, an instance of "LymphNodeResult" is used to store the corresponding result of the test (cf. Figure 8). Furthermore, it is specified to which patient the result belongs and which diagnostic variable has been tested. That means in effect that "resultBelongsTo(LymphNodeResult,MCLPatient)", "testedDiagnosticVariable(LymphNodeResult, LymphNodes)" and "resultValue(LymphNodeResult, 3.0)" are set. Please note that every diagnostic variable is associated with a test and therefore the latter has to be specified explicitly as shown in Section 4.1.

To verify requirements 3 and 4 (cf. Section 1), the instance "SpleenSizeResult" is created (cf. Figure 8). Furthermore, "resultBelongsTo(SpleenSizeResult, MCLPatient)", "testedDiagnosticVariable(SpleenSizeResult, SpleenSize)" and "resultBoolean(SpleenSizeResult, true)" are added. The true value given in the relation "resultBoolean" means that the spleen is affected. Please note that the connected diagnostic

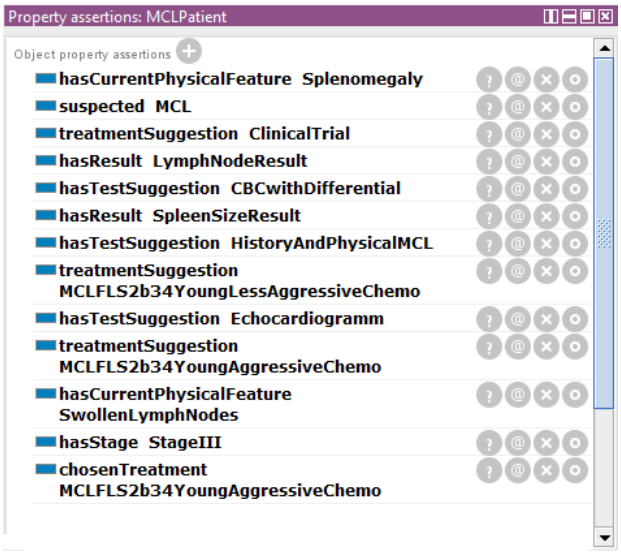

Fig. 8: Property assertions of a sampled MCL patient created on basis of cancer studies [24] after several steps of diagnoses and treatment. Screenshot of the Protégé ontology editor [26].

variable specifies the information of how the relation should be structured in order to indicate the result (cf. Section 4.1).

Given the information about the patient, conclusions can be drawn: e.g., that the example patient has swollen lymph nodes as well as splenomegaly. By this, the medical practitioner is warned in case of abnormal values of the patient, which satifies requirement 3. After completion of history and physical examination, a complete blood count (CBC) is proposed (cf. Figure 8). This corresponds to the judgment of involved medical experts and does not contradict the corresponding CPG [14], also. From this and also from subsequent tests, results can be added (as described above).

For the verification of requirement 4, the stage of the disease present has to be determined. The CPG provides guidance on the determination of the stage – the ontology incorporates this information by axioms which are evaluated as soon as necessary test results are available. Since multiple lymph nodes and the spleen are affected, the example patient is assigned to MCL Stage III (cf. Figure 8).

In accordance to the CPG and medical judgment, the treatment options for MCL Stage III are: aggressive chemotherapy or less aggressive chemotherapy or participation in a clinical trial. These options are proposed to the physician according to requirement 4 (cf. Figure 8). Please note that the sample patient is counted among the younger patients since his age is ≤ 70 years.

In a first step, the medical expert can specify the chosen treatment (e.g. aggressive chemotherapy) by setting the relation "chosenTreatment" accordingly (cf. Figure 8). In further steps the response of the treatment can be specified and treatment suggestions are proposed correspondingly –

this can also involve additional recommendations for examinations which are also part of the treatment process.

Overall, this demonstrates that for the treatment of MCL the requirements 1, 2, 3, and 4 are fulfilled, given an examplary patient. Please note that MM, CML and MDS have also been modeled and verified with similar results. This does not only show that the four modeled complex cancerous diseases can be represented in a suitable manner. We are convinced, because of their prototypical character, the results obtained can also be useful in context of other diseases.

6. Conclusion and Outlook

In this work, Clinical Practical Guidelines of the cancerous diseases Chronic Myeloid Leukemia, Myelodysplastic Syndromes, Mantle Cell Lymphoma, and Multiple Myeloma are modeled.

Their formalization is used for enabling a Decision Support System bridging the gap between theoretical knowledge and practical solutions at the point of treatment. Thereby, ontologies are utilized to represent the incorporated knowledge of the considered guidelines. Because of their prototypical character, the presented modeling approach can also provide valuable insights into the modeling of other cancerous diseases. Verification shows that the requirements for the proposed Decision Support System are fulfilled. For this, exemplary patients are generated which are based on cancer statistics. In this contribution we exemplary presented a verification based on a patient suffering from Matle Cell Lymphoma.

Developing a DSS for daily use requires close collaboration with medical experts who regularly use CPGs. Therefore, we plan to bring our findings into a currently developed software system [27] for further investigation.

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