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ABSTRACT

The DESIREE project has developed a platform offering several complementary therapeutic decision support modules to improve the quality of care for breast cancer patients. All modules are operating consistently with a common breast cancer knowledge model (BCKM) following the generic entity-attribute-value model. The BCKM is formalized as an ontology including both the data model to represent clinical patient information and the termino-ontological model to represent the application domain concepts. This ontological model is used to describe data semantics and to allow for reasoning at different levels of abstraction. We present the guideline-based decision support module (GL-DSS). Three breast cancer clinical practice guidelines have been formalized as decision rules including evidence levels, conformance levels, and two types of dependency, "refinement" and "complement", used to build complete care plans from the reconciliation of atomic recommendations. The system has been assessed on 138 decisions previously made without the system and re-played with the system after a washout period on simulated tumor boards (TBs) in three pilot sites. When TB clinicians changed their decision after using the GL-DSS, it was for a better decision than the decision made without the system in 75 % of the cases.

1. Introduction

On the worldwide level, breast cancer is the most common cancer among women and the second most common cancer. In 2018, two million new cases and more than 600,000 deaths were reported.[1] In France, breast cancer is the most frequent cancer with almost 58,000 new cases per year, in front of prostate cancer, lung cancer, and colorectal cancer with 50,000, 46,000 and 43,000 new cases per year, respectively. After having doubled between 1985 and 2005, breast cancer incidence is globally currently stable in France. More precisely, whereas breast cancer incidence is decreasing for women aged 50–79 who may benefit from the breast cancer national screening program promoted by the National Health Insurance, it is increasing by more than 60 % for women aged 30–49. With 10,000 deaths per year (consolidated figures in 2018), breast cancer mortality is declining in France and breast cancer is one of the best prognosis cancers with among the best five and ten-year survival rates (87 % and 76 %, respectively). However, it still remains a therapeutic challenge especially for triple negative breast cancers and HER2+ breast cancers, for which improvements are both possible and necessary [1].

Clinical practice guidelines (CPGs) are free-text documents developed by National agencies or academic associations to provide the best recommendations for the management of a set of selected patient profiles. These recommendations are built from published clinical research results and represent the state of the art following evidence-based medicine principles [2,3]. Although studies have shown that implementing oncology CPGs does improve clinical outcomes in both overall and recurrence-free survivals of cancer patients [4–11], there

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[1] https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf

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are still variations in clinical practices and the compliance of clinician decisions with CPGs remains low [6,12], e.g., Wöckel et al., reported a 51.9 % compliance rate for the decision of comprehensive care plans for breast cancer patients [6].

In recent years, most countries have implemented organizational measures such as multidisciplinary team meetings or tumor boards (TBs) to promote the shared decision of the various health professionals involved in the management of cancer patients [13]. The goal is to bring together specialists (surgeons, oncologists, radiation therapists, radiologists, pathologists, geneticists, etc.) to discuss each patient case and be able to collectively build the best patient-specific and evidence-based care plan. TBs are also expected to improve CPG implementation as well as clinical trial enrolment. While studies have shown that TBs can improve the compliance of decisions with CPGs [14–16], organization of TBs is hindered by the complexity of discussed patient cases and the amount of information to manage. There is indeed a large number of cases to discuss and finally little time to devote to each of them leading to question the actual impact of TBs on care quality [17–19].

Clinical decision support systems (CDSSs) are health IT tools that require computable biomedical knowledge, person-specific data, and a reasoning or inferencing mechanism that combines knowledge and data to generate and present, at appropriate times, intelligently filtered information to clinicians in order to enhance the quality of their decisions and consequently the quality of the care delivered. While the sole dissemination of free-text CPGs showed to have a low impact on clinician behavior, studies reported that embedding CPGs within CDSSs could improve the compliance of clinician decisions with best practices, in general [20–22] and in the specific case of cancer care decisions made by TB clinicians [23–25].

DESIREE is a European project funded under the H2020 program. The objective is to develop a web-based software ecosystem dedicated to the personalized, collaborative, and multidisciplinary management of primary breast cancer, from diagnosis, to therapy, and follow-up. The DESIREE platform offers some image-based *diagnostic* decision support modalities involving mammogram-based breast density classification [26], fully automated breast boundary and pectoral muscle segmentation [27], and breast mass classification using ensemble convolutional neural networks [28]. Research works on predictive modeling have also been conducted, e.g., to predict the esthetic outcome of Breast Conservative Therapy considering mechanical forces due to gravity, breast density and tissue distribution, and the inflammation induced by radiotherapy and the wound healing [29]. Additional decision support services have been developed to support the *therapeutic* decisions of TB clinicians [30]. The first decision support module is based on the proposal of guideline-based recommendations from patient data. Since CPGs have many flaws [31], e.g., they are incomplete, ambiguous, and do not take into account patient preferences, it happens that non-guideline-compliant TB decisions are legitimate. In this case, they have a clinical value that should be capitalized as another source of knowledge, beyond CPGs. Thus, DESIREE offers a second decision support module based on the experience gained from non-compliant TB decisions [32]. Finally, a third decision support module has been developed based on the implementation of a case-based reasoning process where the goal is to reuse past TB decisions made for patients similar to the new patient case discussed by TB clinicians [33].

The three therapeutic decision support modalities have been implemented within the DESIREE platform as three complementary and interoperable decision support modules, denoted GL-DSS for the guideline-based module, EXP-DSS for the experience-based system, and CB-DSS for the one using the case-based reasoning. We used semantic web tools to implement both GL-DSS and EXP-DSS. More specifically, we have built a breast cancer knowledge model (BCKM) as an ontology used as a conceptual and terminological structure federating the three decision support modules for representing knowledge and patient data [34]. This paper is focused on the presentation of the BCKM and the DESIREE GL-DSS module of the DESIREE platform.

2. The guideline-based decision support module

2.1. Overview of DESIREE components

The DESIREE platform offers several complementary modalities of decision support [30]. If they differ in the knowledge resources they use and the reasoning process they implement, the three decision support modules are articulated around a common knowledge model, the BCKM, represented as an ontology including both the clinical information model and the termino-ontological aspects of the domain to describe data semantics and allow for reasoning at different levels of abstraction. This requires that patient data that feeds decision support modules be consistent with the BCKM.

On the DESIREE platform, the DESIREE information management system (DESIMS) acts as an electronic patient record where patient data is stored in a dedicated database. Through the user interface, it enables patient data entry and output visualization, as well as the control of all DESIREE components implemented as web services. The outputs of the different components are displayed in the user interface using dedicated display presentations. Internally, patient-related data are provided to the different decision support modules using the FHIR exchange format [35] where DESIMS internal data encoding is transformed into a BCKM-consistent representation. Fig. 1 depicts the main interactions between the three decision support modules.

2.2. One ontological model to represent both data and knowledge

The originality of our approach is to represent in the same ontological framework both the clinical information model, i.e., the data model, and the termino-ontological model for the characterization of the application domain concepts. Thus, the BCKM is an explicit specification of all entities and concepts considered as necessary for the management of breast cancer patients. It is a static central resource allowing for interoperability in terms of data structure and semantics. It is also a practical resource to be used by all decision support modules and according to which all data structures and concepts used for the application should be consistently defined. The BCKM is represented as a formal ontology coded in OWL. This allows for the combination of two types of inferences: subsumption-based inferences, i.e., ontological reasoning based on description logic (DL), and arbitrary application of domain-dependent deductions based on production rules.

The structuring of the BCKM ontology replicates the entity-attribute-value (EAV) generic model for data modeling and the integration of concepts related to the breast cancer domain [34]. Thus, the BCKM is not intended to constitute a reference ontology that would cover all aspects of breast cancer, but it rather gathers the body of knowledge required for the computer-based therapeutic management of breast cancer patients. This involves allowing for (i) the representation of patient data collected using an electronic patient record developed outside the DESIREE project, as well as (ii) the formalization and the operationalization of the knowledge embedded within CPGs to provide decision support.

2.2.1. Ontological representation of the EAV data model

Unlike information models dedicated to the biomedical field that offer specific predefined objects for hospital information systems or electronic health records (OpenEHR, FHIR…), the EAV model is a generic model, considered flexible enough to model biomedical data [36–38]. From a logical point of view, data models, whether relational or object-oriented, can be translated into the EAV model. We therefore structured the ontology through the prism of EAV model components and chose to explicitly represent the three elements of the EAV model as classes: entities, attributes, and values.

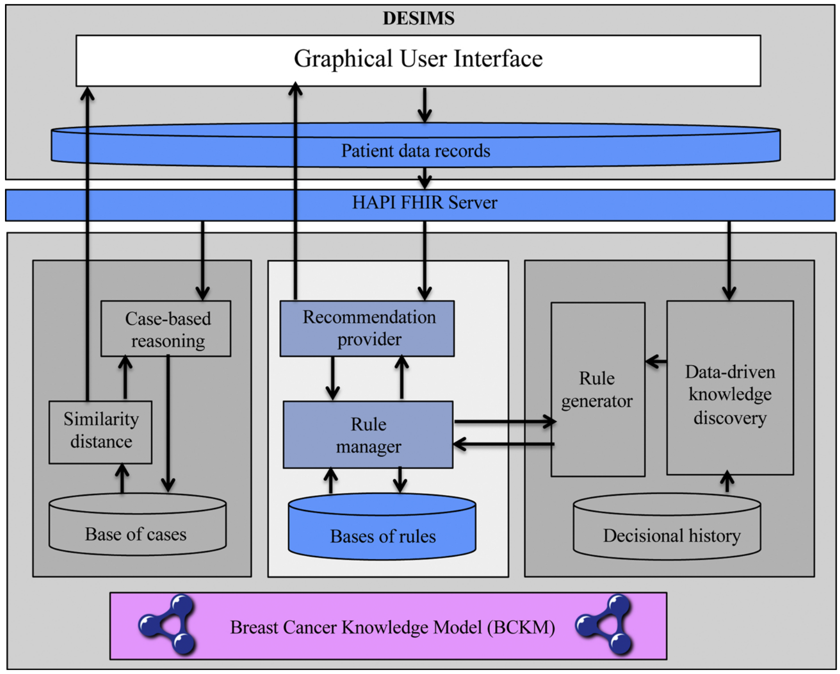

Fig. 1. General architecture and information flows between the different DESIREE decision support modules and the DESIMS.

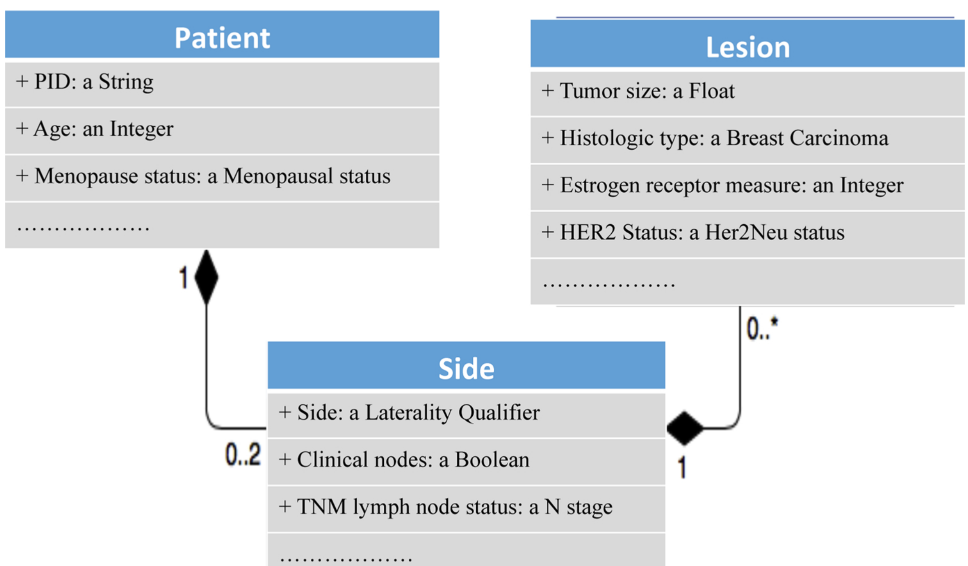

Fig. 2. Excerpt from the UML class diagram representing the three main clinical entities (Patient, Side, and Lesion) used to describe a breast cancer clinical case, and their relationships.

- ModelEntity subclasses are used to define the components of the data model. In our application, they correspond to entities that describe a patient case and are relevant in the decision-making process, e.g., anatomical entities to characterize the disease, the patient (PatientEntity), the side (SideEntity), and the lesion (LesionEntity) (see Fig. 2). Other entities are associated to the patient and characterize her context such as her relatives, prior treatments, and examinations carried out, but also the outcomes issued by the decision support module like recommended care plans or alert messages.
- ModelAttribute subclasses list the attributes of different entities, e.g., the age for the patient (Age), the presence of lymphadenopathies for a side (ClinicalLymphNodes), or the histological type of a lesion (HistologicType). Internally, each class of an attribute is declared to belong to an entity using the object property isAttributeOf.
- ModelValue subclasses represent the different value types declared for attributes. These subclasses correspond to classic primitive types such as integers, floats, booleans, dates, strings. HierarchicalValue is a separate subclass which subclasses are made of discrete value sets structured as hierarchies organized by the subsumption relation. For instance, the two sex values, male and female, are grouped in a flat set of exclusive values, but the types of breast cancer (BreastCarcinoma) are described hierarchically by the set of invasive cancer, in situ cancer, and Paget's disease, each one being refined by more specific subclasses. The interest of these subsumption-structured sets of values is to allow the collection of information at different levels of abstraction and to reason at these different levels. In the ontology, the specification of the value type of an attribute is done by the object property hasRange linking the attribute class and the class of the value type, e.g., the Age attribute of a

patient is linked by hasRange to IntegerValue, the ClinicalLymphNodes attribute to BooleanValue, and the HistologicType attribute of a lesion to the BreastCarcinoma class.
- Relationships between entities are represented by object properties between classes of entities. For instance, a LesionEntity is linked to the SideEntity by the object property hasSide. These data model relationships are sub-object properties of the isRelatedTo object property. This allows for distinguishing between internal object properties and the relationships specific to the data model.

2.2.2. Building the breast cancer knowledge model

Within the DESIREE project, one of the first tasks was to build the application domain model. The elicitation of relevant data elements and their collection were done by combining the expertise of different project partners, such as breast cancer clinicians, electronic health record software developers, guidelines and knowledge representation experts. Among the collected data elements, a subset was referenced as the minimum data set necessary to enable state-of-the-art decision-making in the management of primary breast cancer. This information has been formalized to comply with the BCKM core framework presented above (2.2.1). Four periods of interest or "scenarios" have been identified in the breast cancer management clinical pathway: scenario A when the cancer has just been diagnosed and the decision may be surgery or neoadjuvant therapy, scenario B when a neoadjuvant therapy has been administered and TB clinicians have to decide the surgery or the radiotherapy protocol if the patient is non-operable, scenario C when neoadjuvant therapy and surgery have been administered, and scenario D when surgery has been first performed and adjuvant treatment modalities have to be decided.

The set of concepts related to the application domain is represented as subclasses of the core concepts. Among the introduced concepts, we identified those corresponding to the entities of the data model, such as the patient, the sides, the lesions, the procedures, and the recommendations. We also identified the different attributes characterizing each entity (e.g., age, histological type, tumor size, etc.). Finally, the set of hierarchical values specific to the application domain was integrated into the ontology. As previously said, these sets include both unstructured sets of simple values (sex with male and female values, grade with low grade, intermediate grade, and high grade), and sets of values hierarchically structured by subsumption offering different characterization levels (histological types of breast cancer, TNM classification, breast cancer stages, and all the different therapeutic procedures like surgeries, chemotherapies, and so on). To collect domain-specific value sets, we reused available existing resources, e.g., the National Cancer Institute thesaurus (NCI thesaurus, or NCIt). The NCIt provides a reference terminology for many aspects of cancer management: "it covers vocabulary for clinical care, translational and basic research, and public information and administrative activities."[2]. It includes for each concept textual definitions, several synonyms, relationships with other NCIt concepts including subsumption relationships, and mappings with concepts in other resources like SNOMED CT. Moreover, it is available as an OWL ontology so that some concepts or subclass hierarchies can be reused. Finally, using reference terminologies to build the BCKM is a step towards semantic interoperability with external data sources. On the technical side, we used a tabular ontology tool, named Flat OWL Editor [39], to populate the BCKM. The tool allows to extract concepts and sub-hierarchies from existing ontologies, edit them when necessary, and then insert the updated or new additional sub-hierarchies into the BCKM.

Fig. 3 illustrates the organization of the resulting ontology by distinguishing the core ontology, dedicated to the data model, and the sub-hierarchies of domain concepts stricto sensu.

Fig. 4 displays an extract of the BCKM in Protégé, a popular Open Source OWL Editor [40]. For instance, the concept HistologicType is an attribute (isAttributeOf) of the SideEntity entity and has a value type (hasRange) BreastCarcinoma. The HistologicType concept exists in the NCIt and the information originating from the NCIt is recorded as annotations, like the NCI label, the NCI code, the NCI definition, or the UMLS CUI. Fig. 4 also shows that BreastCarcinoma is a subclass of HierarchicalValue and has subclasses structured as a hierarchy.

2.3. Rule-based knowledge representation

2.3.1. A data model-driven rule language

We used the Natural Rule Language (NRL) [41] as the formalism to specify rules in order to represent guideline knowledge. The IF part of rules checks various constraints on the values of different attributes of the selected entities, including equality tests, numerical comparisons, or subsumption checking with the "is a kind of" operator. Specific logical constructs allow for the negation in rules by checking the existence of complex expressions. The THEN part of rules contains actions that build recommendations (the model of which is described in Section 2.3.2). Fig. 5 provides an example of an NRL decision rule. This rule matches two entities, a side (theSide) of a patient (thePatient). The THEN part is made of the disjunction of two recommended actions. Other NRL constructs in the THEN part allow for the creation of data model components (see Fig. 9).

2.3.2. The recommendation model

The therapeutic management of breast cancer patients is made of a care plan including one or several actions to be performed synchronously or in an ordered sequence. These actions may correspond to different therapeutic modalities (surgery, oncology protocols, radiotherapy plans, etc.) or to any other relevant action like examination, surveillance, referral to a specialist, etc., e.g., 'mastectomy and axillary lymph node dissection' is a care plan made of two synchronous actions, 'systemic chemotherapy, then radiotherapy and endocrine therapy' is a care plan made of sequential actions. Moreover, when a care plan is decided by TB clinicians, the different actions may be described at different levels of abstraction, for instance 'endocrine therapy' or, more specifically, 'tamoxifen therapy', depending on the information available at the moment the clinical case is discussed.

In DESIREE, a recommendation is formally specified in the BCKM and is represented as a care plan. A Recommendation (RecoEntity) is composed of one or several orders (OrderEntity), and each order is linked to one action (ActionEntity). An action is mainly characterized by a BreastCancerProcedure which is the super class for the hierarchy of breast cancer procedures in the BCKM. In addition to the action, an order is characterized by several important attributes or relationships as displayed in Fig. 5:

- The *step* to specify the rank of the action in the ordered sequence. In Fig. 5, the step is '1' to represent the first action of a sequence.
- The *entity* on which the action has to be performed, for instance a chemotherapy is performed on the patient, whereas mastectomy and re-excision are performed on the side.
- The *evidence level* of the action as provided in CPGs. For instance, NCCN guidelines propose categories of evidence where the highest level is 1, the default is 2A, and the lowest is 3 [42].
- The *conformance level* to indicate what is the expected conformance of end-users with the action. We adopted a classical qualitative six-value scale with SHALL when the action is required, SHOULD when the action is recommended, MAY when the action is possible, along with their negative counterparts SHALLNOT, SHOULDNOT, and MAYNOT.

As previously said, clinical knowledge, including guideline knowledge, can be described at varying levels of abstraction based on the information available on a patient. For example, CPGs recommend that

[2] https://ncithesaurus.nci.nih.gov/ncitbrowser/

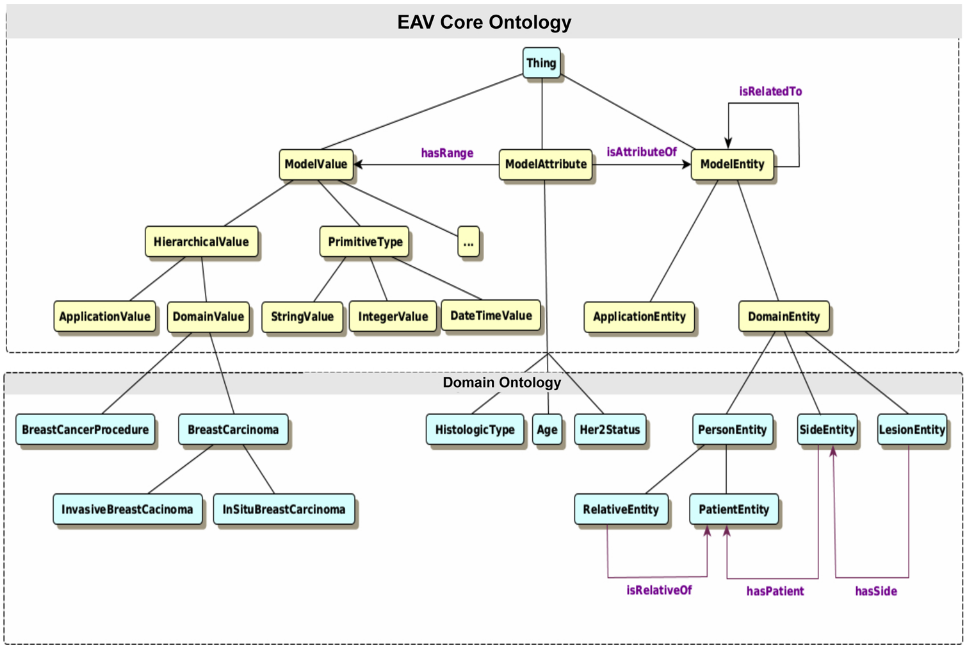

Fig. 3. Structuration of the top of the core ontology with domain concepts integrated at the bottom.

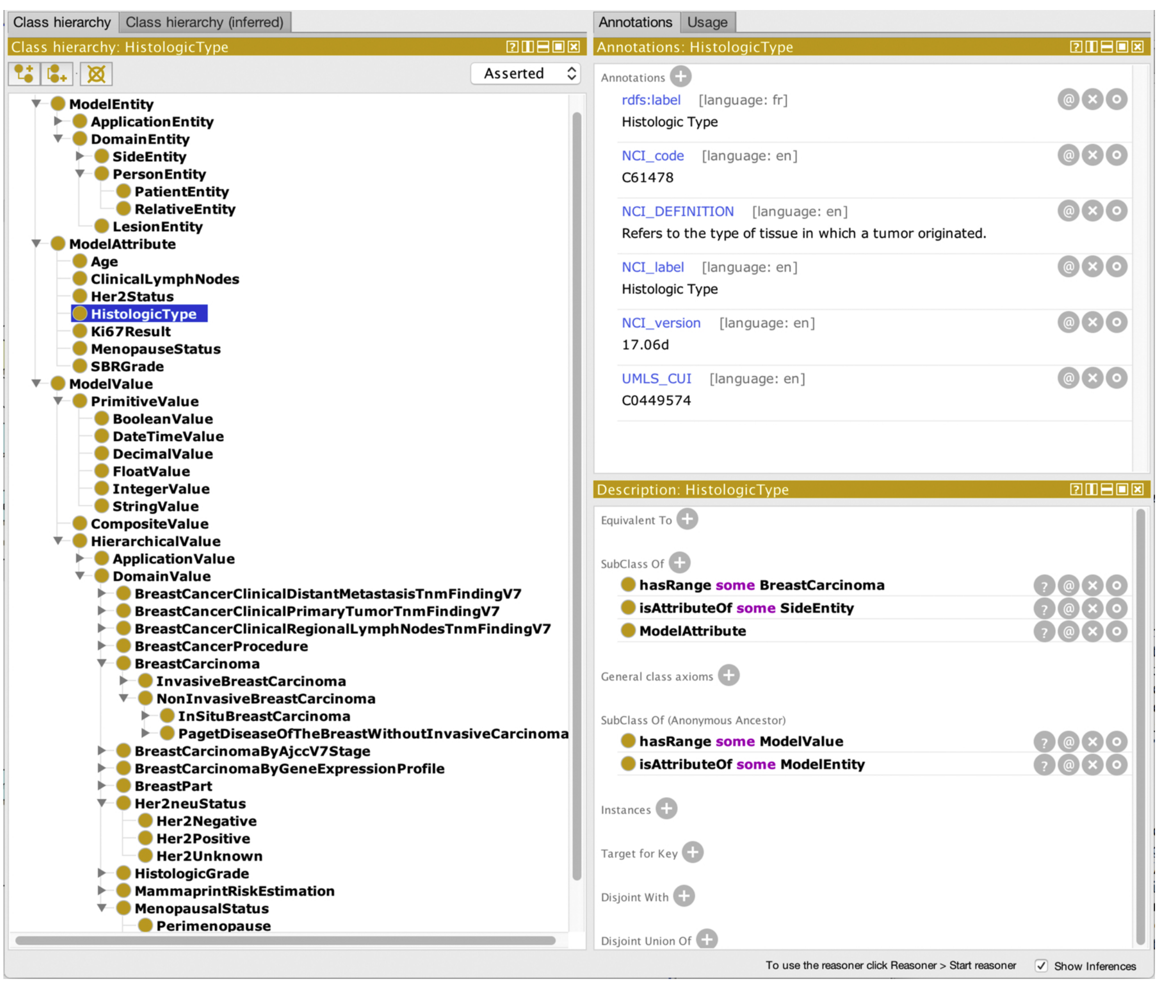

Fig. 4. Extract of the BCKM ontology in Protégé.

```
Context: PatientEntity
--
Action Rule: "Scenario D: IF in situ breast cancer AND prior breast conservative surgery
AND surgical margins ≤ 2mm THEN Re-excision is recommended (p13) OR Mastectomy
is possible (p13)"

    "theSide" is a SideEntity,
    "thePatient" represents theSide.hasPatient,

IF
        thePatient.BUScenario = ScenarioD
AND     theSide.BreastHistologicType is a kind of InSituBreastCarcinoma
AND     theSide.PriorBreastConservationSurgery = true
AND     theSide.InSituCarcinomaMarginWidth <= 2

THEN
  [buildRecommendation] from
    [build] OrderEntity with BreastReExcisionForPositiveMargins to theSide
        with ' 3' using 'SHOULD' step 1,
  [buildRecommendation] from
    [build] OrderEntity with Mastectomy to theSide with '2A' using 'MAY' step 1;
```

Fig. 5. Example of an NRL decision rule to exemplify the consistency with the BCKM.

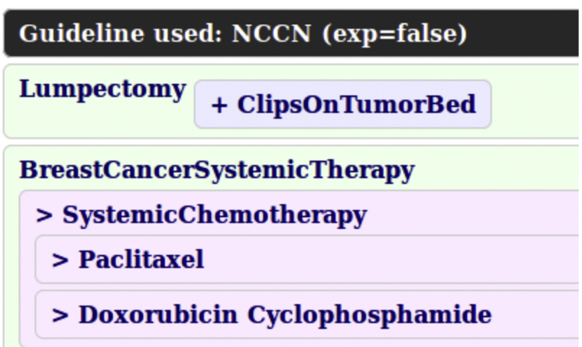

Fig. 6. Illustration of complement and refinement dependencies between recommendations.

a surgical axillary exploration be performed for invasive breast cancers. If axillary lymph nodes are not invaded, the surgical axillary exploration is a sentinel lymph node biopsy, otherwise it is an axillary lymph nodes dissection. Formal rules have been built following the same pattern. We have proposed to enrich recommendations produced under a given context by the provision of two types of dependencies between an order and a new recommendation, a "refinement" relationship and a "complement" relationship. In the first case, the new recommendation includes an order with a more specific action, whereas in the second case, the action is complemented by another recommendation. Fig. 6 illustrates the two dependencies, with the example of lumpectomy complemented (noted with a '+') with clips on the tumor bed, and the systemic therapy refined as a systemic chemotherapy, itself refined by two chemo protocols, paclitaxel and doxorubicin-cyclophosphamide.

Two operators have been added in the THEN part of the rule language to create recommendations that depend on an order of a recommendation (AddComplementReco and AddRefinementReco). Fig. 7 provides two rules used to generate some dependent recommendations according to the two variants of the example provided in Fig. 6.

2.4. Clinical practice guidelines modeling

2.4.1. Formalization of CPG knowledge

The preliminary step was to select international breast cancer management CPGs to cover the worldwide state of the art as well as the "local guidelines" currently implemented by DESIREE clinical partners. This step resulted in the selection of several CPGs among which three were encoded in an executable format: NCCN© guidelines published by the network of 27 cancer centers in the United States [42], internationally considered as reference guidelines, and two local guidelines, the French recommendations published by the Assistance Publique - Hôpitaux de Paris (AP-HP) [43], and the recommendations published by Onkologikoa, both being clinical partners of the DESIREE project. Thus, we encoded the three CPGs to be used as knowledge bases for decision support, with (i) the chance to reduce the decision support silence when CPGs are complementary and some CPGs may provide recommendations to fill in the knowledge gaps of the others, and (ii) the risk to increase decisional conflicts when CPGs are inconsistent and recommendations provided by the ones are in contradiction with recommendations provided by the others.

In a way similar to the DeGel approach [44], the translation from free-text CPGs to computer-interpretable guidelines was performed in several steps, from free text (original CPGs), to semi-structured text, semi-formal text, and a formal, machine-executable representation. These different steps are listed below using the example of re-excision in the case of an *in-situ* breast cancer as displayed in Fig. 8.

- The first step aims at building a human-readable semi-structured version of CPG contents as IF-THEN statements keeping the reference to where the recommendation was quoted in free-text guidelines, the evidence level (EL) when available, and the expected conformance level. This step was performed by a medical oncologist specialized in the management of breast cancer (CP). Then, rules were validated by clinical partners (CN, LT). In the example displayed in Fig. 8, we obtained:

  "IF In situ breast cancer AND prior Tumorectomy performed AND there is a lesion with margins smaller than 2 mm THEN re-excision by Tumorectomy is recommended (EL = 3, p13) OR Mastectomy is possible (EL = 2A, p13)"

- The second step is based on the completion and standardization of the notions used in the rules according to concepts defined in the knowledge model to reach a semi-formal version of CPGs. This led to rewriting the rules in a pseudo-logical language that remained nevertheless understandable by clinicians. This step was performed by a medical computer scientist with a good knowledge of the management of breast cancer (BS). The previous statement was rewritten as follows with BCKM concepts:

```
Context: PatientEntity
--
Action Rule "Example of complement"

       "theLesion" is a LesionEntity,
       "theAction" is a ActionEntity,
       "theOrder" represents theAction.hasOrder,
IF
        thePatient.BUScenario = ScenarioAC
AND theOrder.hasObject = theLesion
AND theAction.hasOrder = theOrder
AND theAction.Action = Lumpectomy
AND theOrder.Conformance is one of 'SHOULD', 'MAY'

THEN
   [AddComplementReco] theOrder from
     [build] OrderEntity with ClipsOnTumorBed
            to theLesion with '2A' using 'SHOULD' step 1;
```

```
Context: PatientEntity
--
Action Rule "Example of refinement"

       "thePatient" is a PatientEntity,
       "theAction" is a ActionEntity,
       "theOrder" represents theAction.hasOrder,
IF
        thePatient.BUScenario = ScenarioAD
AND theOrder.hasObject = thePatient
AND theAction.hasOrder = theOrder
AND theAction.Action = BreastCancerSystemicTherapy
AND theOrder.Conformance is one of 'SHOULD', 'MAY'

THEN
   [AddRefinementReco] theOrder from
       [build] OrderEntity with SystemicChemotherapy
            to thePatient with '2A' using 'SHOULD' step 1;
```

Fig. 7. Two examples of rules that generate dependent recommendations in the context of an existing recommendation (complement on the left side, refinement on the right side).

"IF InSituBreastCarcinoma AND PriorBreastConservationSurgery AND InSituCarcinomaMarginWidth < = 2 THEN BreastReExcisionForPositiveMargins using 'SHOULD' with 3 OR Mastectomy using 'MAY' with 2A"

- The third and last step aims at encoding the rule in a way that guarantees that the rule description is consistent with the BCKM, the NRL syntax, and DESIREE workflow. This requires to identify the relevant attributes and entities for describing the IF part of the rule and to check the correct object argument for specifying the recommended actions. The resulting formal NRL rule encoding the recommendation presented in the first two steps is the rule given in Fig. 5. A condition about the patient scenario has been added (thePatient.BUScenario = ScenarioD). The other conditions are expressed with attributes of the *side* entity. For instance, the BreastHistologicType attribute indicates the histologic type of the cancer at the *side* level, an information which is not provided from raw patient data but was inferred from the anatomopathological description of all lesions in the side (in case of multiple lesions). This pattern is used in many rules to synthetize or abstract information which is required at a high level of abstraction to match guideline knowledge but not directly available in raw patient data. Fig. 9 illustrates a rule that performs abstraction at the *side* level of raw data given at the *lesion* level. Moreover, it exemplifies the use of existential quantifiers. The rule reads: "IF the histologic type at the side level is not known, AND there exists at least one lesion of the same side which histologic type is a kind of in situ cancer, AND there is no lesion of the same side which histologic type would be invasive cancer, THEN the histologic type at the side level is in situ cancer".

2.4.2. Structure and organization of rule bases

For each CPGs, e.g., NCCN CPGs, AP-HP CPGs, or ONK CPGs, we have built a structured knowledge base formalized as NRL rules. If the NRL syntax allows for grouping sets of rules, this aims at structuring the authoring process and has no impact on rules execution. However, we needed to distinguish two kinds of rules, which implicitly yields two subsets: a set of generic rules, independent from CPGs, and a set of guideline-specific rules.

Generic rules describe common knowledge of the breast cancer domain. Most of these rules abstract or synthesize information from raw data at the same entity level, for instance by inferring a new categorial value for an attribute from an existing numerical value of another attribute of the same entity, or by inferring a new entity-attribute-value triple from a more complex situation involving different entities as exemplified in the rule displayed in Fig. 9. The role of these rules is to infer a synthetic representation of the clinical case to enable guideline-specific knowledge to be triggered. This is especially used in the case of entities linked with a part-of relationship, like a lesion, part of a side, part of a patient, to raise the information from one level to the upper ones, e.g., raise the in situ histologic type of a lesion to the in situ histologic type of a side (if there is no other invasive lesion in the side) (see Fig. 9). Such rules are necessary to properly handle the cases of multifocal cancers (with multiple lesions in the same side) and/or of bilateral cancers (when both sides have the disease). These common rules can be used with the rule bases that represent the different CPGs.

On the contrary, guideline-specific rules encode specific guideline contents and mostly generate recommendations when conditions expressed on the synthetic clinical case are satisfied, as the rule in Fig. 5 exemplifies: "theSide.BreastHistologicType is a kind of InSituBreastCarcinoma AND theSide.PriorBreastConservationSurgery = true AND theSide.InSituCarcinomaMarginWidth < = 2" means that the patient is suffering from an in situ breast cancer (there is no invasive lesion) managed by a breast conservative surgery and that there is at least a margin lower than 2 cm (or exactly one if there is only one lesion). In this case, according to AP-HP CPGs, surgical re-excision is recommended, mastectomy is possible.

2.5. Implementation

2.5.1. Execution engine

Combining ontological reasoning and custom rules has been studied for long (e.g., [45]) and there exist many tools that enables the two types of inferences with different approaches. In our case, since the rules are written in NRL, one requirement was to be able to implement the source NRL constructs we used in the destination rule language of

C – Surgical re-excision indication

• Margins

- In situ cancer, surgical margins ≤ 2 mm
- Invasive cancer: unclear inked margins

All indications for re-excision must be discussed in tumor boards.

Fig. 8. Excerpt from the AP-HP textual CPGs – March 2016, p. 13 (translated).

```
Context: PatientEntity
--
Action Rule "R-COMMON: IS Breast cancer side"
--
        "theSide" is a SideEntity,
IF
                theSide.BreastHistologicType is not present
        AND     there is a LesionEntity ("aLesion")
                    where (aLesion.hasSide = theSide AND
                           aLesion.HistologicType is a kind of InSituBreastCarcinoma )
        AND     there is no LesionEntity ("anotherLesion")
                    where (anotherLesion.hasSide = theSide AND
                           anotherLesion.HistologicType is a kind of
                                                InvasiveBreastCarcinoma )
THEN
        set theSide.BreastHistologicType to InSituBreastCarcinoma;
```

Fig. 9. Example of a rule abstracting information: the histologic type is abstracted at the side level from data given at the lesion level.

the tool. Basically, rule-based reasoning relies on the closed world assumption where negation is treated by negation as failure. This is not the case with pure DL-based reasoning based on the open world assumption. We needed to use both reasoning types to deal with rules and data as required by the project. Especially, the first type was required to handle an NRL operator like "there is no", as used in the rule displayed in Fig. 9. We chose to use the EYE semantic reasoner [46] which, unlike SWRL, allows constructs like "not exist" or "for all". EYE is written in Prolog and is able to deal natively with triples in the N3 notation [47]. Data and rules are provided to EYE in N3. Considering ontological reasoning, the OWL DL semantics in EYE is managed by explicit rules which are executed together with custom rules in an homogeneous integration framework. Moreover, according to the authors, EYE is reported to be quite efficient on several benchmarks.

Using EYE as the execution engine for the GL-DSS required that patient data, NRL rules, and the BCKM be expressed in N3 to feed the engine. N3 being through the Turtle syntax just another serialization format for the OWL ontology, transforming the BCKM in N3 was quite straightforward. However, the transformations of data and rules required dedicated and consistent parsing. From the user point of view, NRL custom rules corresponding to some given CPGs are executed in a forward-chaining mode by saturation and generate patient-centered recommendations.

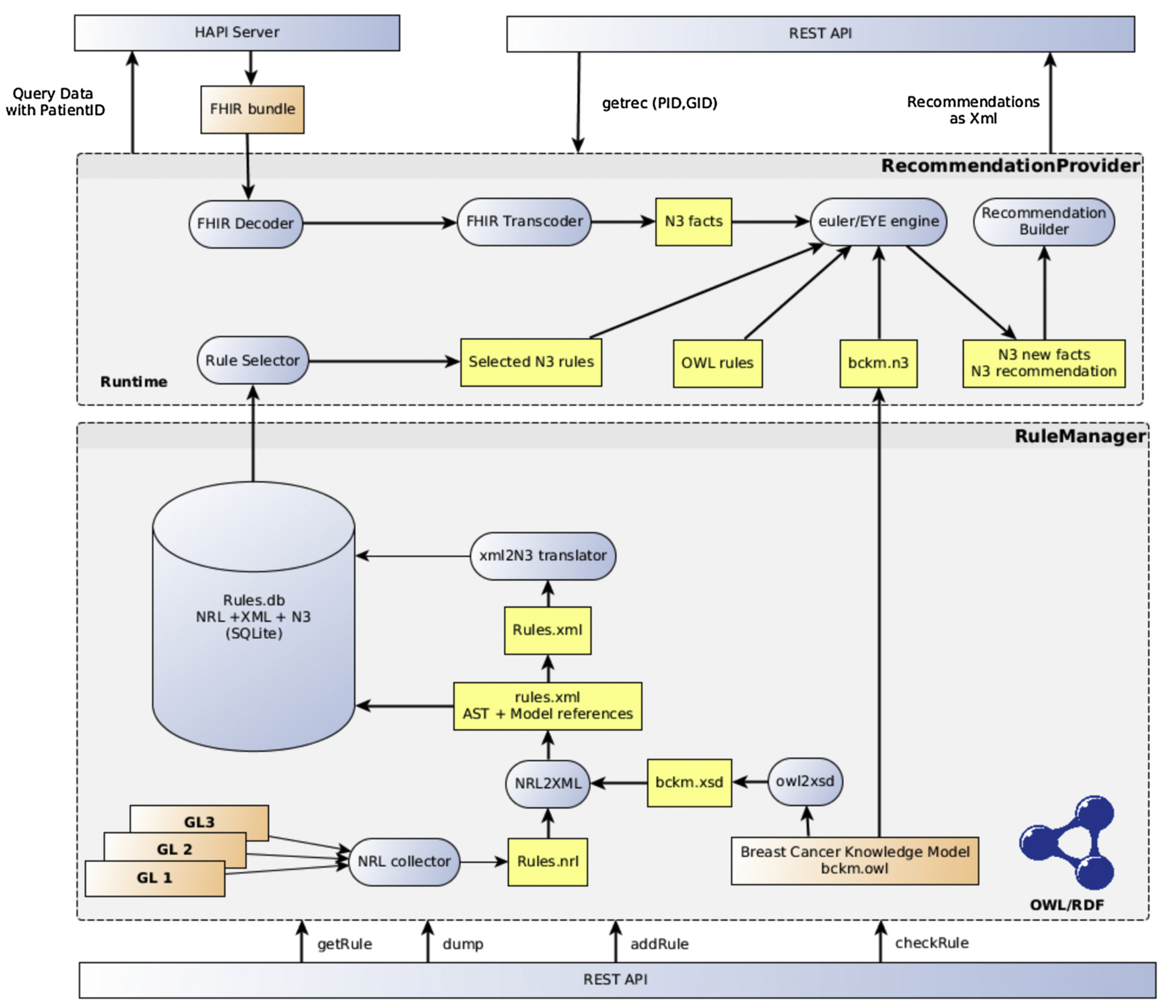

Fig. 10. General scheme and visualization of knowledge and data flows within the GL-DSS engine.

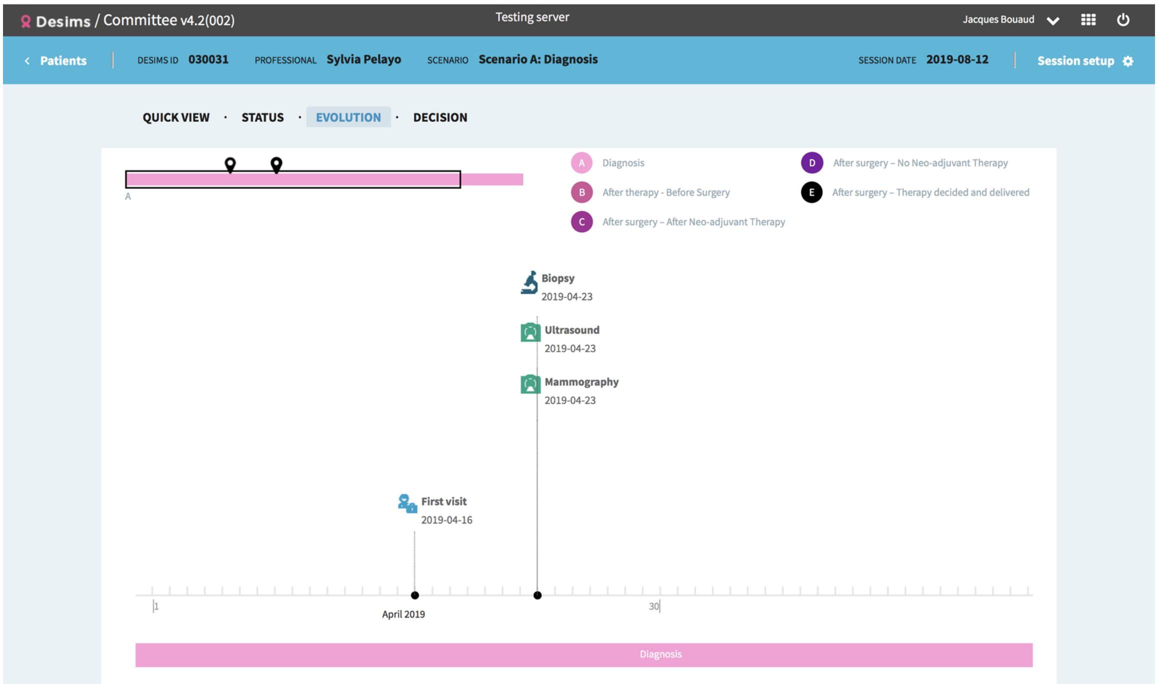

Fig. 11. Time-line display of the different events of the patient clinical pathway.

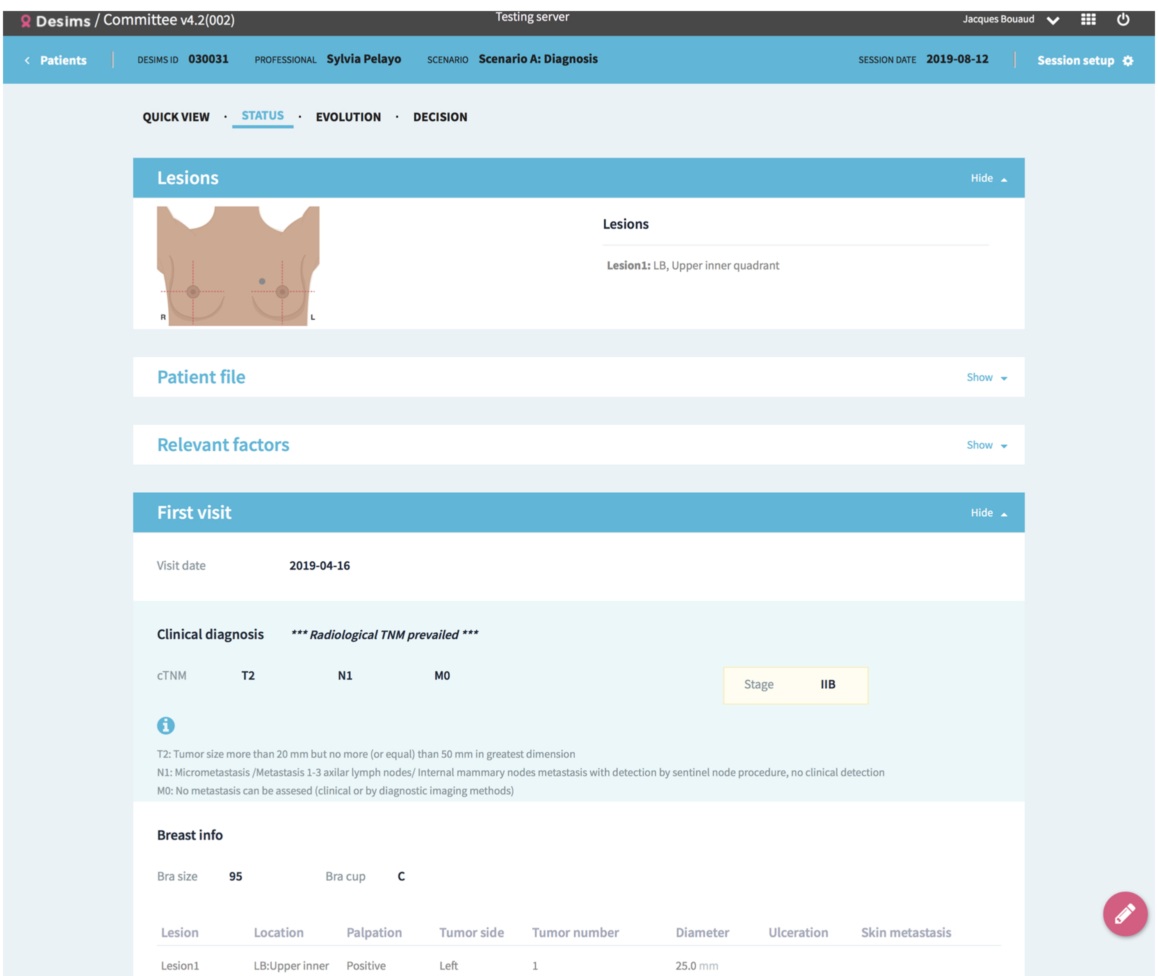

Fig. 12. Screenshot of DESIMS showing a summary of patient data.

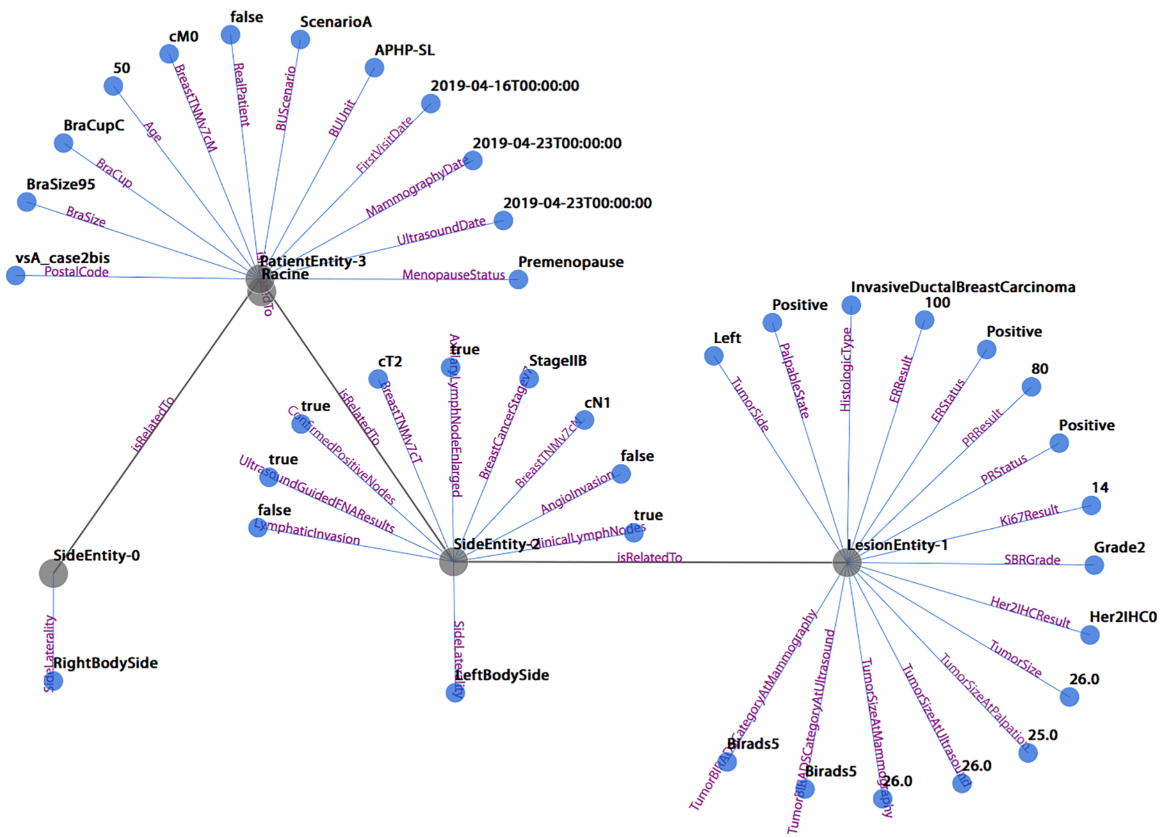

Fig. 13. Graph-based representation of the instantiated data model for the described clinical case.

2.5.2. Rule management

A rule manager component has been developed to handle and store the different rule bases. A rule base usually corresponds to the formal version of CPGs, but in DESIREE, a rule base could also originate from the experience-based decision support (EXP-DSS) that learns rules from decisions made in a given clinical site that do not comply with CPGs [32]. Fig. 10 provides a schema of the rule manager workflow. Since NRL is a data model-driven language, the NRL parser requires an explicit data model specification to check the syntax of NRL rules. This reference data model is an XSD model which is automatically derived from the BCKM. The parser can then validate the rules when they are consistent with the BCKM. Once correctly parsed, rules are transformed into an intermediate XML representation similar to the Knowledge Artifacts specification proposed by the HL7 organization [48]. The principle promoted by this approach is to propose a shared knowledge representation independent of the source rule expression language (NRL in our case) and independent of the rule execution language (N3 in our case). The XML representation is also used to exchange rules with the EXP-DSS which generates EXP-based rules in this format that are stored in the rule manager [32]. Finally, the XML rule representation is transformed into N3, the target internal representation of rules, in order to be executed by EYE. The rule manager is implemented as a web service, a tomcat servlet, and its internal rule repository is a basic SQLite database.

2.5.3. Generation of recommendations

The recommendation provider is the main component of the GL-DSS and its role is to deliver the recommendations issued for a given patient case following some given CPGs. The recommendation provider is implemented as a tomcat servlet. Data flows generating guideline recommendations are displayed in Fig. 10.

Patient data is stored in the DESIMS in a proprietary database. For interoperability reasons, the DESIMS provides patient data to the different decision support modules through FHIR bundles using a limited number of FHIR resources (Patient, Observation, Body Site, Specimen, Careplan, etc.). For a given patient, all patient-related entities, their attributes, and their values are transferred with a coding scheme consistent with the BCKM in a FHIR message which is stored temporarily on a HAPI FHIR server. The semantic interoperability between the DESIMS and the BCKM is implemented through DESIMS-BCKM code mappings. When the recommendation provider is called with a patient ID, a FHIR decoder is responsible for fetching and parsing the patient's bundle from the HAPI FHIR server. Then the FHIR transcoder translates patient data into N3 triples consistent with the BCKM organization.

From the guideline ID provided as an argument to the recommendation provider call, a rule selector requests the rule manager for the corresponding rule base in the N3 format. Depending on the call arguments, different guidelines can be used (NCCN, AP-HP, or ONK), as well as different sets of experience-based rules. Then the inference engine is executed using these selected N3 rules, the N3 representation of the patient, the N3 representation of the BCKM, and the OWL DL rules provided by EYE.

As a result, the engine produces a set of new triples inferred by the application of the selected rules. This set of triples is transferred to the recommendation builder which extracts from the triple graph the list of structured recommendations as described in 2.3.2 and generates an XML output which, besides the recommendations, also includes the list of triggered rules and the new inferred facts. This output is then returned to the caller, in practice the DESIMS. The whole process is described with a clinical case in the next section.

Fig. 14. Visualization of the recommendations produced by the GL-DSS for the described clinical case.

3. Results

3.1. Qualitative and quantitative information about the BCKM and the rule bases

In the current state, the conceptual model built for DESIREE relies on 22 entities and a total of 394 attributes. Attributes are distributed according to their value type as follows: 49 % Booleans, 9 % integers, 4 % floats, 5 % strings, 4 % dates, and 33 % refer to hierarchical values. The resulting BCKM ontology contains 1445 classes, 2305 axioms, 25 object properties, 15 data properties. A total of 658 classes are derived from the NCI thesaurus.

NCCN CPGs for breast cancer are among the most utilized comprehensive breast cancer guidelines. The 2017 version of NCCN CPGs is made of a comprehensive document of 199 pages, 75 pages of "blocks" describing decisional algorithms, and 124 pages of narrative guidelines. The more recent breast cancer CPGs from AP-HP (France) have been published in 2016 as a 36 page-long document describing both diagnostic and therapeutic recommendations making the difference between surgery, chemotherapy, and endocrine therapy procedures. Onkologikoa CPGs appear as a set of eight blocks displaying the recommended management of the most frequent breast cancer presentations. The three CPGs have been first structured as a set of human-readable decision rules, then encoded in NRL. The whole process resulted in three rule bases made of a total of 386 rules for NCCN CPGs, 305 for AP-HP CPGs, and 494 for ONK CPGs. Rule bases share the same subset of common generic rules made of 12 rules.

3.2. Using DESIREE on a clinical case

3.2.1. Case description and data entry

We consider the case of a 50-year-old woman, in pre-menopause, with a left breast lesion of 25 mm at palpation and a left axillary lymphadenopathy. Mammography has revealed a lesion in the upper inner quadrant of the left breast, 26 mm, BI-RADS 5. Ultrasound confirmed a 26 mm lesion, the biopsy of which diagnosed a ductal invasive carcinoma, grade 2, estrogen receptor 100 %, progesterone receptor 80 %, HER2 negative, Ki67 at 14 %. The fine needle aspiration of the axillary lymph node retrieved positive tumor cells. Cancer is classified as cT2N1M0, stage IIB. Data has been entered using DESIMS, (the EHR of the DESIREE project). The different procedures already performed can be visualized on a time line as depicted on Fig. 11.

Fig. 12 shows a screen shot of the DESIMS interface summarizing the status of the patient with a focus on the most important data to be reminded before decision is made by TB clinicians.

Fig. 13 shows the graph based on the triple representation of the instantiated data model that describes the clinical case and which is used as input for the decision support modules after patient data has been transmitted from the DESIMS via FHIR.

3.2.2. Production of recommendations

The GL-DSS is launched from the DESIMS user interface. The user

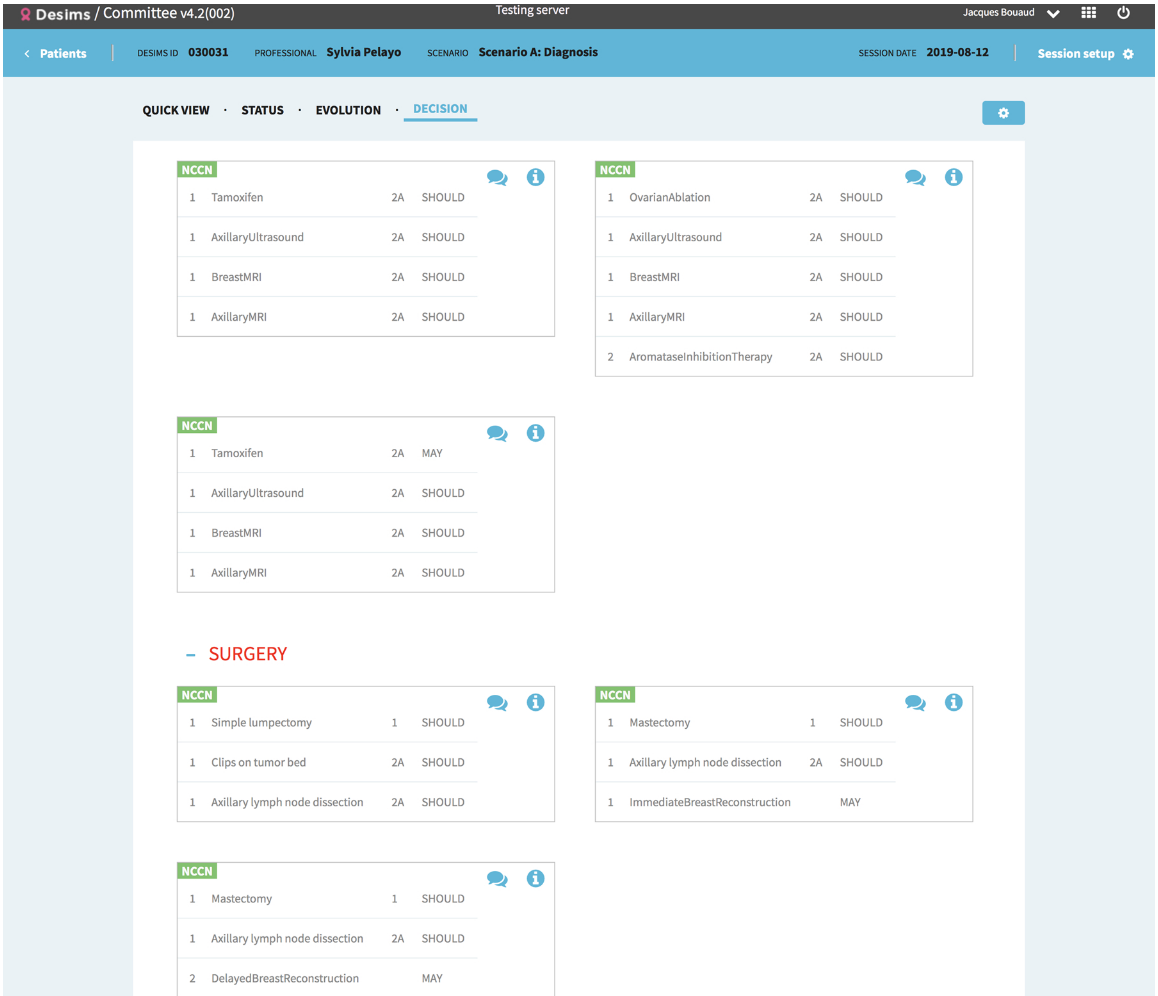

Fig. 15. Display of the recommended care plans in the DESIMS.

Table 1
Preliminary results of the clinical assessment of the GL-DSS by the three clinical pilot sites.

	# TB clinicians	# TB sessions	# Decisions	Compliance of $D_{without}$	Compliance of D_{with}
ONK	3	6	86	98.8 %	96.5 %
ERE	3	3	17	100.0 %	100.0 %
AP-HP (GPEH)	3	5 (+ 3)	35	100.0 %	97.1 %
Total	9	14 (+ 3)	138	99.3 %	97.1 %

may interactively choose the CPGs she wants the GL-DSS to consider for the decision support (NCCN, AP-HP, ONK). A number of recommendations are then returned and displayed to TB clinicians which may either decide to follow one of the suggestions or, if not, enter their final decision. For instance, when the GL-DSS is launched on the clinical case described above with NCCN CPGs, several different concurrent therapeutic options are provided, basically two surgeries and multiple options of systemic neo-adjuvant therapies. Fig. 14 provides an illustration of the XML recommendation nested structure returned by the GL-DSS and made of:

- At the first level, a recommended lumpectomy (with a conformance level “SHOULD”) associated with a recommended axillary exploration, *refined* as an axillary lymph node dissection while the lumpectomy is *complemented* by the placement of clips on the tumor bed;
- At the first level, a recommended mastectomy (SHOULD) associated with a recommended axillary exploration, *refined* as an axillary lymph node dissection, and *complemented* with an optional breast reconstruction (conformance level “MAY”), which can be *refined* into either an immediate breast reconstruction or a delayed breast reconstruction;
- The third option for this patient is a neo-adjuvant systemic therapy, which is refined into several recommended (SHOULD) or optional (MAY) chemotherapy protocols along with endocrine therapy, which can be refined as Tamoxifen therapy.

Finally, recommendations are displayed in the DESIMS user interface (see Fig. 15) at the most specific level by flattening the initial nested recommendation structure. From our example, the first surgery option is made of a block tagged with the guideline ID, i.e., “NCCN”, where procedures (lumpectomy, clips on the tumor bed, and axillary lymph node dissection) are listed with their evidence level and conformance level.

3.3. Clinical evaluation

A clinical evaluation of the DESIREE platform was performed in July 2019 by all the clinical partners of the project, Onkologikoa (ONK, a cancer center located in San Sebastian, Spain), ERESA (ERE, providing diagnostic imaging and radiotherapy, Valencia, Spain), and Assistance Publique – Hôpitaux de Paris (AP-HP, the first cancer care institution in Paris region and France, with the Georges Pompidou European Hospital, GPEH, as the pilot site). We report in this paper the preliminary results of the clinical evaluation of the sole GL-DSS prototype.

The GL-DSS was evaluated by three clinical pilot sites (ONK, ERE and GPEH). All sites selected a sample of past retrospective clinical cases previously discussed in real TBs without the GL-DSS and for which $D_{without}$ decisions were recorded. The past clinical cases used were different from one clinical site to the other. For the evaluation, the past clinical cases were anonymized and re-discussed in close to real (simulated) TBs (meetings involved at least the three mandatory medical specialties for breast cancer decisions, a radiotherapist, a medical oncologist, and a surgeon) and D_{with} decisions were collectively made using the GL-DSS (each pilot site worked on its own past clinical cases). Prior to the beginning of the evaluation, a short user training video has been presented to TB clinicians to describe (i) the main functionalities of the whole DESIREE platform, with a focus on (ii) how to register a patient for a TB, (iii) how data describing clinical cases are organized in the DESIMS, and (iv) how the GL-DSS should be used.

Seventeen simulated TBs were organized (among which three encountered technical problems such as delays in response times for different reasons), each one included three clinicians, and a total of 138 D_{with} decisions were recorded for 110 different patients. The compliance rate of $D_{without}$ decisions with GL-DSS recommendations was very high, i.e., 99.3 % and the compliance rate of D_{with} decisions with GL-DSS recommendations remained at the same very high level (97.1 %). The few non-compliant decisions with the GL-DSS were mainly explained by some flaws in the interface (i.e., the DESIMS was actually displaying the recommendation finally decided by TB clinicians, but because there were too many recommendations, clinicians did not manage to retrieve them from the interface, or TB clinicians wanted to choose two recommendations but this was not allowed). The comparison of $D_{without}$ and D_{with} decisions showed that clinicians modified their prescriptions 24 times out of 138 decisions when using the GL-DSS (i.e., in 17.4 % of the cases). An external expert in the domain of breast cancer management assessed the quality of $D_{without}$ and D_{with} decisions and established that D_{with} decisions were strictly better decisions than $D_{without}$ decisions in 18 cases out of 24 (in 75 % of the cases), e.g., "Endocrine therapy" without the GL-DSS and "Tamoxifen therapy" with the GL-DSS. A summary of the results is displayed in Table1.

At the end of the simulated TBs, we performed a qualitative analysis. TB clinicians were asked to complete the User Experience Questionnaire [49] and to answer some questions about the added value of the system, what they especially appreciated, what they especially disliked, what would be the barriers and the facilitators for using the system in the future during TBs. Qualitative data was also extracted from the recordings of TB sessions. Results showed a very positive evaluation of the GL-DSS from the clinicians regarding the attractiveness and ease of use of the system. For instance, Fig. 16 illustrates with a word cloud the clinicians' answers to the question "What did you especially appreciate in the GL-DSS and why?". Perceived as promising and easy to learn, the GL-DSS system caught the interest of clinicians who declared they were ready to use it in a daily practice if the system is extended to manage more "complex" patient cases. The current version was perceived as rather useful for non-expert centers.

Fig. 16. Word cloud synthesizing answers to the question "What did you especially appreciate in the GL-DSS and why?".

4. Discussion and conclusion

The GL-DSS of the DESIREE project is a guideline-based CDSS applied to the management of breast cancer patients. Supporting the implementation of CPGs by CDSSs has a long history. The first CDSSs applied to the management of breast cancer patients date back to 1986 [50]. These systems were expert systems with knowledge bases formalizing the expertise of clinicians engaged in decision-making tasks. Since then, various CDSS prototypes have been developed for the management of breast cancer. Most of them are guideline-based systems to support the decisions of TB clinicians, e.g., MATE [24], OncoCure [51], and OncoDoc [52,25]. More recently, systems such as IBM's Watson for Oncology [53] or the Oncology Expert Advisor [54] seek to build oncology decision support tools using artificial intelligence components trained on data extracted from scientific literature (querying bibliographic databases such as PubMed) and retrospective TB decisions. However, results are controversial and IBM's Watson for Oncology has come under fire for not delivering on expectations to provide state-of-the-art personalized treatment for cancer patients and for producing advice that is "unsafe and incorrect" [55,56]. To the authors' knowledge, if breast cancer CDSSs have been assessed on retrospective real patient data with high rates of agreement between TB decisions and the CDSS's recommendations (93.2 %, 85.2 %, 93.4 %, and 93 % for Mate [24], Oncocure [51], OncoDoc [25], and Watson for Oncology [53], resp.), a few oncology CDSSs have been actually routinely used during TB meetings except OncoDoc2 [23], and only a small number demonstrated that they did improve the compliance of TB decisions with CPGs (e.g., Oncodoc2 showed to have a compliance rate of 91.7 % [25]). A recent systematic review [57] showed that few studies have assessed the outcomes of CDSSs for oncology practice, and has concluded on the critical need for CDSSs development and evaluation. Aiming at developing a breast cancer CDSS improving existing systems, the GL-DSS of the DESIREE project is in line with these two objectives.

Different formalisms have been used to represent CPG contents in breast cancer guideline-based CDSSs. For instance, Mate [24] uses the PROforma language based on the CREDO software platform [58]. In Oncocure [51], CPGs are encoded using Asbru that represents clinical guidelines and protocols as time-oriented skeletal plans [59]. OncoDoc [25] proposes a documentary approach to breast cancer decision support where the user may navigate through a knowledge base structured as a decision tree to get the best patient-specific recommendations. Using semantic web technologies, Abidi et al. [60] developed a web-based execution engine to combine the ontology representing CPGs and associated domain knowledge, and the patient ontology describing the patient's state. More generally, numerous dedicated formalisms have been proposed to translate free-text CPGs into computer-interpretable guidelines [61,62]. In the GL-DSS of the DESIREE project, we have used the Natural Rule Language [41] as the formalism to specify rules in order to represent guideline knowledge. Inspired by OCL (Object Constraint Language), and originally designed as a language for testing the validity of data models [63], NRL provides a syntax for writing logical expressions consistent with the data model components, independently of the specification of an execution engine. NRL rules are then transformed in N3 notation, the target computer-interpretable guideline formalism to be used by the semantic inference engine, EYE, combining ontological reasoning and rules. Using tools from the semantic web domain as a base could have led to some kind of solution based on SWRL rules associated to a classical OWL reasoning engine to produce inferences. However, because of the lack of expressiveness of the latter, the impossibility to deal with non-monotonicity and negation within the open world assumption and the degraded performances obtained on real-life applications with these techniques, we chose to adopt an alternative solution with Euler/EYE which does not have these limitations. Besides, this approach allows a reasoning process able to produce therapeutic treatment recommendations with varying levels of abstraction for the patients whose clinical profiles can also be described at varying levels of abstraction. The design of the BCKM was done in the context of the development of a research prototype with the strong constraint of representing real data from the DESIMS (that relies on a relational model). We chose to use the EAV data model, which is simple but generic and flexible enough to model biomedical data [36–38]. In addition, we chose to explain each element of the EAV model as classes and not exploit the OWL possibilities where attributes could have been represented by DataProperties for primitive types and ObjectProperties for hierarchical types. This class representation allows to import concepts / classes from other ontologies and to give them any role in the BCKM: entity, attribute, or value. Thus, we have imported many concepts and hierarchies from the NCI thesaurus to the BCKM using the Flat OWL Editor tool [39]. It should be noted that in this case, the link between the NCI thesaurus and its cloned classes is not dynamically conserved as it can be the case with a tool such as OntoFox [64] but it is static with the NCI_CODE kept as annotation. However, we did not look for the dynamic preservation of the import link, first because we did not consider that the structuring of the NCI thesaurus was satisfactory for our application (the organization of some hierarchies had to be reviewed manually), and second, the coding of existing data for certain versions of the BCKM and its concepts might not be able to withstand the evolutions of the BCKM, which should be controlled. In the current state, the quality of the BCKM is quite satisfactory since it allows to represent information, both DESIMS-provided patient data and guideline knowledge, in a way that enables decision-making and automatic production of recommendations with a good level of performance, as established by the technical and clinical validation steps of the GL-DSS.

Interoperability of medical data is essential to improve care quality and efficiency, and there are multiple standards available for clinical data exchange, e.g., the Consolidated Clinical Document Architecture (C-CDA) and the Fast Health Interoperability Resources (FHIR) maintained by Health Level 7 (HL7). Unfortunately, the data collected in health information tools is often in a non-standard, non-structured, or even non-coded (text) form, resulting in a lack of interoperability. The main issue for CDSSs is to get patient data originally input into electronic health records (EHRs). For instance, MATE [24] contains its own data entry facilities for its stand-alone EHR. Concerning OncoDoc [25] and Abidi's work [59], all patient data are entered as needed in the decision process and there is no linking with an EHR, while OncoCure [51] is integrated into an existing EHR used at the point of care, relieving the user from data entry. In the DESIREE project, the DESIREE Information Management System (DESIMS) acts as an EHR where patient data is stored in a dedicated database. However, the DESIMS was designed prior to the DESIREE project, with an information model different from the one adopted in the BCKM and an equally different terminology repository. While the use of FHIR has made it possible to solve the syntactical dimension of interoperability, semantic interoperability required manual alignment between the terms used in the DESIMS repository and the BCKM concepts. This finding calls for the sharing of termino-ontological references, but also models of clinical information [65], possibly dedicated to a particular area such as cancer [66]. In addition, beyond classic semantic interoperability issues, TB decisions are the result of collective discussions and, although based on CPGs, they do take into account a variety of "holistic parameters" [51] that may not be directly represented in EHRs, such as complex, implicit, hard to codify knowledge, or individual patient preferences. No holistic parameters were included in the DESIMS data model whereas some of them were part of the BCKM. As a consequence, the reasoning process performed by the GL-DSS was reduced because some holistic patient data were missing due to the DESIMS filter. Since we chose to explain each element of the EAV model as classes, we have started to experiment another solution to reinforce interoperability between EHR-like components used to collect patient data and the GL-DSS. Indeed, having classes to represent each element of the EAV model makes the hasRange relationship between a ModelAttribute class and a ModelValue class generic and allows to process it uniformly regardless of the value type. This feature has been exploited for the automatic construction of input forms from the ontological BCKM, to be used as integrated EHR-like interfaces [67]. Beyond re-enforcing interoperability, this has also been used to explore the whole potential of the GL-DSS reasoning process on non-simple clinical cases including holistic parameters not considered by the DESIMS.

All published guideline-based breast cancer CDSSs rely on the modeling and implementation of a single CPG applied to a unique pathology, the management of breast cancer. Since computer-interpretable CPGs are built from the translation of free-text guidelines, they import some of the natural language weaknesses, and even with only one disease, guideline-based decision support systems have to deal with intra-CPGs inconsistencies. This difficulty is even more important when handling the concurrent application of CPGs for different diseases in order to manage patients with comorbidities. Galopin et al., [68] have implemented an ontological reasoning process to allow for the flexibility necessary to deal with patients suffering from both hypertension and type 2 diabetes. Wilk et al. [69], have proposed a framework based on first order logic to represent CPGs and to mitigate possible adverse interactions (drug-drug or drug-disease) between the recommendations provided by the different CPGs. Abidi et al., [70] proposed the CPG integration framework COMET to manage multiple CPGs using comorbidity management procedures based on the input of domain experts. In these cases, CPGs are reconciled on the basis of competition and the goal is to select the recommendations that are "best suited" to the patient complexity. In the DESIREE project, we chose to use three CPGs (NCCN, AP-HP, and ONK) to support the decision of the clinical partners of the project with the provision of their local guidelines, but also to offer to all of them the possibility to get recommendations from international CPGs and to extend the clinical coverage of the GL-DSS [71]. Indeed, we know that there are some knowledge gaps in CPG contents that lead to the silence of the CDSS for the specific profiles not covered by CPGS. Thus, the bet was that even if we used contemporary CPGs versions (all CPGs embedded within the GL-DSS were published in 2017), knowledge gaps of some CPGs could be filled in by the others. This has been confirmed in the special case of NCCN and AP-HP CPGs where the silence of one CPG was resolved by the other CPG to allow the GL-DSS to provide recommendations in 21 % of the cases [72]. As opposed to the management of multiple CPGs in case of polymorbid patients, the aim was to reconcile breast cancer CPGs on the basis of complementarity. In addition, reconciliation solutions have been developed within the decision rules (complement and refine). But we have to develop a post treatment of the recommendations provided to solve the conflicts and build care plans from atomic recommendations while benefiting from the complementarity of CPGS.

The GL-DSS module of the DESIREE project aims at providing decision support at different levels of abstraction, allowing for flexibility in the reasoning process. We presented the developments we made and justified our choice to use semantic web tools. We constructed a single domain ontology used as a conceptual and terminological structure to provide a data model and a knowledge model, used for reasoning and decision support. The resulting BCKM plays a pivotal role in data and knowledge management. Other studies aim at combining information models and ontologies [73,74]. The GL-DSS of the DESIREE project has been implemented in the basis of three CPGs (NCCN, AP-HP, and ONK). It has been assessed during simulated TBs in three pilot sites on 138 decisions. It appeared that the clinical cases used for the clinical validation were simple cases with a high rate of TB decisions compliance with CPGs. This high rate was conserved when using the system to solve the same clinical cases. However, the quality of TB decisions was improved when using the system for 18 clinical cases out of the 24 where TB clinicians changed their decision. This result has to be confirmed with a larger study involving complex clinical cases in AP-HP real-life TBs. Prior to this evaluation, our future works would be to develop the prerequisites to achieve a true interoperability between the AP-HP EHR system (Orbis from Agfa[3]), to implement the reconciliation of CPGs to solve decisional conflicts, and to build care plans from atomic recommendations. We especially would have to develop an algebra of atomic recommendations conformance levels to compute the conformance level of the inferred care plans.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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