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Ten years of knowledge representation for health care (2009–2018): Topics, trends, and challenges

David Riaño[a,*], Mor Peleg[b], Annette ten Teije[c]

[a] Universitat Rovira i Virgili, Tarragona, Spain
[b] University of Haifa, Haifa, Israel
[c] VU Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Background: In the last ten years, the international workshop on knowledge representation for health care (KR4HC) has hosted outstanding contributions of the artificial intelligence in medicine community pertaining to the formalization and representation of medical knowledge for supporting clinical care. Contributions regarding modeling languages, technologies and methodologies to produce these models, their incorporation into medical decision support systems, and practical applications in concrete medical settings have been the main contributions and the basis to define the evolution of this field across Europe and worldwide.
Objectives: Carry out a review of the papers accepted in KR4HC in the 2009–2018 decade, analyze and characterize the topics and trends within this field, and identify challenges for the evolution of the area in the near future.
Methods: We reviewed the title, the abstract, and the keywords of the 112 papers that were accepted to the workshop, identified the medical and technological topics involved in these works, provided a classification of these papers in medical and technological perspectives and obtained the timeline of these topics in order to determine interest growths and declines. The experience of the authors in the field and the evidences after the review were the basis to propose a list of challenges of knowledge representation in health care for the future.
Results: The most generic knowledge representation methods are ontologies (31%), semantic web related formalisms (26%), decision tables and rules (19%), logic (14%), and probabilistic models (10%). From a medical informatics perspective, knowledge is mainly represented as computer interpretable clinical guidelines (43%), medical domain ontologies (26%), and electronic health care records (22%). Within the knowledge lifecycle, contributions are found in knowledge generation (38%), knowledge specification (24%), exception detection and management (12%), knowledge enactment (8%), temporal knowledge and reasoning (7%), and knowledge sharing and maintenance (7%). The clinical emphasis of knowledge is mainly related to clinical treatments (27%), diagnosis (13%), clinical quality indicators (13%), and guideline integration for multimorbid patients (12%). According to the level of development of the works presented, we distinguished four maturity levels: formal (22%), implementation (52%), testing (13%), and deployment (2%) levels. Some papers described technologies for specific clinical issues or diseases, mainly cancer (22%) and diseases of the circulatory system (20%). Chronicity and comorbidity were present in 10% and 8% of the papers, respectively.
Conclusions: KR4HC is a stable community, still active after ten years. A persistent focus has been knowledge representation, with an emphasis on semantic-web ontologies and on clinical-guideline based decision-support. Among others, two topics receive growing attention: integration of computer-interpretable guideline knowledge for the management of multimorbidity patients, and patient empowerment and patient-centric care.

1. Introduction

In 2009, Silvia Miksch, Mor Peleg, David Riaño, and Annette ten Teije organized the first international workshop on knowledge representation (KR) for health care (KR4HC) in Verona, Italy [1]. The main purpose was to satisfy the need of a lacking scientific forum where new advances on the representation and exploitation of medical knowledge could be presented and discussed by the members of the

* Corresponding author.
E-mail address: david.riano@urv.cat (D. Riaño).

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Table 1
KR4HC editions: year, location, number of attendees, submissions, long paper acceptances, published papers (including long, keynote and invited papers), and post-proceedings references.

Year	Location	#Attendees	#Submissions	#Accepted long	#Publications[a]	Post-Proc
2009	Verona, IT	32	23	11	15	[1]
2010	Lisbon, PT	20	14	10	11	[2]
2011	Bled, SI	36	22	10	12	[3]
2012	Tallin, EE	28	22	9	12	[4]
2013	Murcia, ES	41	19	10	11	[5]
2014	Vienna, AT	27	26	7	10	[6]
2015	Pavia, IT	44	27	5	10	[7]
2016	Munich, DE	20	12	6	8	[8]
2017	Vienna, AT	27	15	3	11	[9]
2018	Stockholm, SE	–	28	9	9	In [10]

[a] Including keynote and invited papers, after a peer review.

community of artificial intelligence in medicine. The great success of the event with 32 registrations, 23 submitted works, 11 of which (48%) were accepted for long presentations and selected as best papers for publication [1], encouraged us to continue with subsequent yearly meetings as summarized in Table 1.

The success of the publications and their interest were also measured in terms of the number of downloads per year of the papers contained in the post-proceedings.[1] These are shown in Fig. 1, distinguishing the download years in different colors (see legend).

Along the 2009–2018 years, KR4HC settled as a meeting to present new advances and experiences in the principles, languages, technologies, methods, computer intelligent systems, and applications of knowledge representation and engineering to confront medical and clinical problems. A peer-review process based on the evaluation of papers by at least two experts with a focus on the clinical importance, originality, quality, interest, and maturity of the proposals was followed. The focus on health-care knowledge representation makes it a unique event in its specificity and different from other broader meetings such as the conferences Artificial Intelligence in Medicine (AIME), Computer-Based Medical Systems (CBMS), Medical Informatics Europe (MIE), or the American Medical Informatics Association Annual Symposium (AMIA).

After a decade of KR4HC, we considered worth making a retrospective analysis of all the works presented in the workshop with the purpose of identifying the main topics and their trends, but also to detect recurring clinical and technological challenges of knowledge representation for health care.

Our approach followed the identification of medical as well as technological topics contained in the papers. For the medical topics, we wanted to determine which were the prevalent medical problems and specialties which knowledge representation is applied to. For technological topics, we aimed at delimiting the theories, languages, technologies, methods, systems, and tools, based on KR, which were most applied to health-care. We were also interested in the identification of the maturity of the presented works.

2. Methods

The titles, the abstracts and the keywords of all the papers published along the ten years of the workshop [1–10] were extracted and analyzed. We looked for explicit indications on the knowledge representation structures used, their contribution to the knowledge life cycle, the clinical issue addressed, the maturity of the work, and the diseases targeted. For the knowledge structures, we distinguished between those coming from the broad artificial intelligence field, such as rules, ontologies, or Bayesian Networks, adapted to deal with medical issues, and those arising from other communities, notably the Medical Informatics community, where specific formalisms such as computer-interpretable guideline languages or semantic codification of clinical terms were developed to represent health care knowledge. We extracted all the relevant descriptive topics of the papers contained in their titles, abstracts, and lists of keywords. The complete list of topics found are provided in the Appendix.

We then held several sessions to determine a meaningful emerging structure to organize the papers into a hierarchy of topics. This hierarchy is shown in Table 2 and it emerged from the organization of the topics when these were grouped into classes of similar or related concepts. We identified the specific papers addressing each topic, and noted their total number per topic, per year, and the overall number of papers per topic. A given paper could address multiple topics.

The analysis of topics stressed the most prevalent topics, but it also contemplated other less frequent topics that could be complementary or relevant to consider. In these cases, the papers with the less frequent topics were read in order to determine whether their contribution justified the consideration of the topic, or not.

Using their year of publication, the papers related to each topic were distributed along the ten years under consideration. The timeline progression of the number of papers per year with regard to each topic was analyzed in order to determine the level of variability, the special production years, and the progression of each topic. The results can be sensitive to collateral causes such as the selection of papers during the review process, which was very restrictive and therefore prone to leave multiple studies unselected for publication and consequently out of the current analysis. In this sense, results should be taken cautiously and not necessarily representative of the whole field of knowledge representation in health care, but only the reflection of this field in ten years of the KH4HC workshop.

After the study, each one of the authors was engaged in the identification of ongoing and emerging challenges of knowledge representation for health care. A selection of the most prominent emerging ones was discussed and agreed by the three authors.

3. Results, discussion, and challenges

The hierarchy of topics in Table 2 determines six primary dimensions for analysis: the knowledge representation methods used, the medical informatics representations provided, the contributions to the knowledge life cycle, the clinical emphasis, the level of development, and the diseases addressed. In this section, we discuss the papers along these six dimensions. Some dimensions can be mutually related and, consequently, they may show some overlapping or complementarity. We also expose the results on the temporal progression of the topics found in the papers, in order to identify their trends and remark some challenges of knowledge representation for health care for the future.

[1] Official information by Springer (books [1–8]) on concluded years. Notice that downloads of [1] started in 2010.

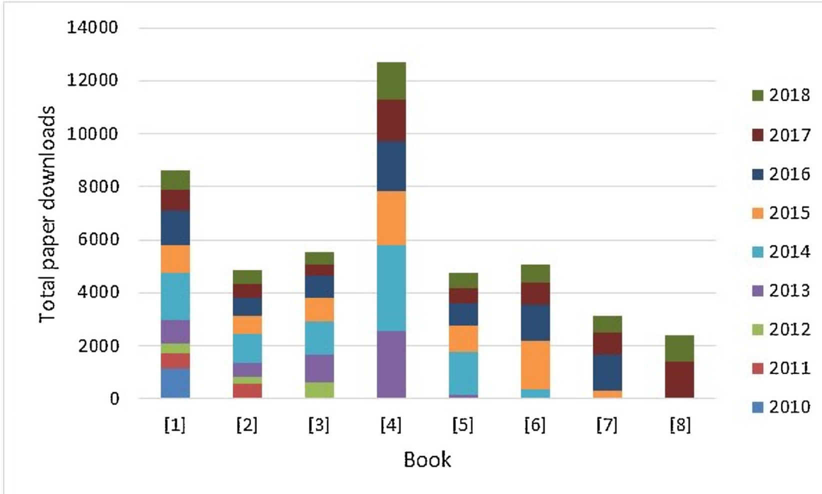

Fig. 1. Number of paper downloads per year for each post-proceedings. Each bar shows the total number of downloads broken down in colors by the number of downloads in each year.

Table 2
Hierarchy of topics found after the analysis of the KR4HC papers.

Knowledge representation methods I: Generic
Ontologies
Semantic methods
Semantic Web, semantic relation(ships), semantic approaches
OWL
SPARQL, semantic queries
Decision tables and rules
Logic formalization
Temporal Logic
Answer Set Programming (ASP)
Temporal abstraction
Probabilistic models
Decision tree
Markov model
Bayesian network
Knowledge representation methods II: Medical-Informatics specific
Computer-Interpretable Guidelines (CIG)
Asbru, GLIF, ProForma, GLARE, GELLO
Electronic Health/Patient Record (EHR)
HL7/HL7-RIM, OpenEHR, Archetypes
Medical vocabulary
UMLS, SNOMED-CT, MeSH, ICPC, ICD
Knowledge Life Cycle
Knowledge generation
Knowledge specification
Exception detection and management, quality assessment, and critiquing
Knowledge enactment
Temporal knowledge and reasoning, knowledge-based temporal data abstraction
Knowledge sharing and maintenance
Clinical emphasis
Treatment
Diagnosis
Clinical indicators
Guideline integration for multimorbidity patients
Level of development
Formal level
Implementation level
Testing level
Deployment level
Diseases
Cancer
Circulatory system illnesses
Chronicity
Comorbidity

3.1. Generic knowledge representation methods used

According to [16], the field of knowledge representation contains a number of important types of representation, some of which are present in the ten years of KR4HC workshops. The four most prominent representation types observed are: ontologies with 22 papers, semantic web-related papers with 19 (actually 9 overlap with ontologies papers), decisions tables and rules with 14 papers, 10 logic-related papers, and several probabilistic approaches like decision trees, Markov models and Bayesian networks. Below we discuss the main contributions of the papers in these categories.

3.1.1. Ontologies

Ontologies are a knowledge representation formalism in which concepts in a domain, their properties, relations, and restrictions are formally established. Ontologies and taxonomies play a role over the entire time span of ten years of KR4HC workshops. A number of papers contribute to the knowledge representation field by developing new generic methods; for instance, in [17] the authors present an automatic, unsupervised and domain-independent approach for structuring the resources available in an electronic repository, and in [18] two methods are explored for partitioning large medical vocabularies.

Other papers apply ontology mapping and alignment techniques in a medical setting [19,20], use ontologies for the annotation of radiology and notably mammography reports [21], interoperability [22–24], or classification of medical actions [25]. Some works develop specialized ontologies for representation of domain knowledge, care flows, or pathways, or for supporting the detection and mitigation of clinical guideline interactions [26,27,20,28–31,73,77,83,87].

3.1.2. Semantic Web, semantic relations, semantic approach; OWL; SPARQL, queries

During the entire period (2009–2018), 19 papers were related to semantic web technology. Semantic Web is a way to provide data in the Internet with a meaning that allows automatic interpretation and processing by machines. This shows an evident overlap (9) with ontologies papers, in the subsection above. Here, we discuss the most important contributions with regard to semantic web. We start with the papers where integration plays a relevant role and continue with a number of medical applications of the semantic web technology.

Authors in [23] discuss the prospects and challenges for semantic enhancements consisting of annotations as OWL axioms,[2] which commit to an upper-level ontology that provides categories, relations, and constraints for domain entities and informational entities. They

[2] The Web Ontology Language (OWL) is the official language for the Semantic Web.

show how ontologies can improve semantic interoperability in health care.

Paper [17] presents an unsupervised and domain-independent approach for structuring the resources available in an electronic repository. The obtained taxonomy was then tested against the MeSH taxonomy used in PubMed, and it outperformed other existing taxonomic search engines based on clustering techniques.

For translational research, the integration of phenotype and clinical data is crucial. The work in [42] integrates phenotype descriptions from text-rich research sources and clinical data from experimental and clinical practice. In [67], the same authors use semantic web technology for interoperability by semantic integration of heterogeneous data in clinical trials, and to facilitate automatic reasoning and data processing services for decision support systems in various settings of clinical trials.

The authors of [52] claim that the quality indicators can be automatically computed when the indicators are regarded as semantic queries that retrieve the patients who fulfill certain constraints. OpenEHR archetypes were used to semantically integrate patient data and quality indicators [22]. Archetypes allows formal definition of clinical information in terms of information constraints for health care data reuse.

Applications in the context of clinical guidelines are also detected. Representation and execution of clinical practice guidelines using OWL ontologies and SPARQL-based inference rules are discussed in [86,87]. SPARQL is a language to manipulate RDF[3] data in the Web. Paper [53] uses semantic web technologies to evaluate care actions from computer interpretable guidelines and to detect potential contradictions in the personalization process, while [56] uses semantic web technology for reasoning with a hierarchy of medical actions and treatment data to detect dominant alternative interventions in order to analyze feasible cost reduction. Self-management is the application of semantic web in [30] where a social cognition theory is modelled in the form of an OWL-DL ontology. Paper retrieval is the application in [85,88].

Applications related to natural language were also observed. In [47], the authors use UMLS and in particular its Semantic Network to detect patterns in clinical guidelines. Based on semantic relations, those patterns can be used for several tasks like guideline modelling or compliance. In [84], authors exploit free text sources via natural language processing and linked data. It is a nice application in detection of adverse drug reaction (ADR) signals using data retrieved from PubMed and Twitter.

The last remarkable paper in this category is [89]. This paper emphasizes that the impact of linked data and linked open data on healthcare information systems has been limited, in comparison with other sectors.

3.1.3. Decision tables and rules

Decision tables and rules are approaches to specify which actions to perform depending on given conditions. They are used to specify rules that domain experts use to reach a decision based on the values of (clinical) parameters. These formalisms are observed during all ten years of KR4HC. Rules were used to process medical records to discover possible cases of hospital acquired infections [44]. Decision tables containing medical knowledge and the physician's experience were used to deal with medical questions that need to be answered frequently [50]. Decision tables were also used to summarize differential diagnosis by exploiting the diagnostic knowledge contained in guidelines [78]. A third application of decision tables is in the ICU, for the simulation of the evolution of different sorts of shocks while patients are treated [79,94].

Rules were used for a variety of medical tasks. Firstly, rules were used to identify potential contradictions in the personalization of clinical processes due to patient's preferences or comorbidities [[53.59]], or to represent and manage medical exceptions that may occur during the enactment of a patient-centered care pathway [66]. Another application of rules was to help automate the process of modelling a clinical guideline [68,25]. In [74], authors showed how rules can be used to detect the level of evidence in medical guidelines. Lastly, in [93,95] rules were used to facilitate the assessment of adherence to clinical guidelines (in particular, temporal constraints) based on patient data records.

3.1.4. Logic (temporal, probabilistic, answer set programming, temporal abstraction)

Several logic-based frameworks are given in the papers, in particular for clinical guidelines. In [36], the authors propose to use temporal logic to formalize clinical guidelines augmented with physiological background knowledge (to capture the dynamics of the processes using qualitative knowledge), while in [48], temporal reasoning is combined with a probabilistic reasoning for the management of care.

Several papers use logic in order to allow the combination of knowledge from several guidelines into consistent care plans for patients with multimorbidity. Paper [74] presents a framework for applying multiple clinical practice guidelines to comorbid patients that relies on a first-order logic-based representation and related theorem proving and model finding techniques. An answer set programming (ASP) based method is proposed for detecting and repairing conflicts between treatments, in [87]. ASP is a logic-programming framework to deal with complex search problems. ASP is used in [90] as well, for the comorbidity problem of interaction among guidelines. The authors of this paper complemented their conformance analysis with an explanation component, and paid particular attention to the temporal dimension. In [91], the analysis of the interactions between guidelines was based on temporal representation of clinical facts and their distribution in time to support for interaction detection.

The use of temporal patient data remains challenging and also the use of nowadays available genomic data. Authors of [92] explore temporal abstraction and statistical significance to determine biological significance.

3.1.5. Probabilistic models: (decision trees, Markov models, bayesian networks)

There has been a number of probabilistic models in the KR4HC workshops, like decision trees, Markov models or Bayesian networks. Broadly speaking, decision trees represent decision procedures by means of concatenation of questions whose answers drive the decision in one or other direction, which are the branches of the tree. Markov models are probabilistic tools that allow prediction of evolution in state-changing systems. Bayesian networks are probabilistic graphical models representing conditional dependencies among variables to predict the likelihood of event occurrence. These are discussed later, in Section 3.3.

The above knowledge representation techniques are useful in a variety of medical tasks, as shown. Notice that most of the authors do not claim to contribute to the field of knowledge representation, instead they apply knowledge representation techniques.

3.2. Medical informatics-specific knowledge representations

The three dominant medical informatics foci on which the KR4HC community has been developing special representations are clinical guidelines or clinical pathways (computer-interpretable clinical guidelines (CIG[4]) [102], electronic health/patient records, and medical

[3] The Resource Description Framework (RDF) is a standard model for data interchange and merging on the Web.

[4] Computer-Interpretable Guidelines (CIG) are the implementation of clinical practice guidelines for computer-based clinical decision support.

domain ontologies). In particular, the topic of representing and reasoning with clinical guidelines is intensively studied (e.g., [37,46,54,61,68,73,83,87]). In some years, for instance 2009, 2014, 2015 and 2017, more than half of the papers had to do with clinical guidelines. Languages devoted for clinical guideline representation have been used, mainly Asbru (e.g., [25]), GLIF [19], Proforma (e.g., [37]), GLARE (e.g., [35]), and GELLO [19], which is a standard for representing clinical guideline criteria –a topic that all of the CIG formalisms need. Co-morbidity and thereby the interaction among guidelines is studied by several groups (e.g., [72,73,90]). Some works address clinical pathways. These are a (multidisciplinary) activity-oriented specification of best-practice management plan or protocol that is applicable to a particular patient population for a specific period [14]. These works include [20,63,64].

There is a whole set of papers which takes into account the representation of the electronic health/patient record (e.g., [46,103,61,22]). The standards like HL7/HL7-RIM are often used [19,38,53,61,31], and also the standardization with OpenEHR and archetypes [46,61,22,62,93].

The most highly used medical vocabularies are UMLS [33,41,47,53,62,66,68,25], SNOMED-CT [34,22,62,72,74,93], MeSH [100], and the International Classification of Primary Care (ICPC) [34]. These vocabularies are used for mapping protocol elements [32,93] or computer interpretable guideline elements [19,46,24] to patient health records. Authors of [34] developed a Consumer-oriented Medical Vocabulary and aligned the ontology with the International Classification of Primary Care (ICPC).

3.3. Contribution to the knowledge life cycle

According to [102], there is a life-cycle to knowledge generation and usage, which includes a series of processes, as Fig. 2 summarizes, starting with knowledge generation, followed by knowledge specification, exception detection and management, quality assessment and critiquing, knowledge enactment, temporal knowledge representation and reasoning, and finally knowledge sharing and maintenance. We used this life-cycle approach to review the collection of KR4HC papers.

3.3.1. Knowledge generation

Some papers describe works about the production of knowledge. This knowledge can be mined from the available data sources or elicited from experts. In the first case, you may use machine learning (ML) or case-based reasoning (CBR). In the second case, knowledge can be acquired with tool-assisted methods or with qualitative methods, which are based on interviews or focus groups. With machine learning, health care data can be transformed into probabilistic models such as decision trees [43], Bayesian networks [69], Markov models [45,75,98], or rules [50], among others, that allow to capture a wide variety of knowledge concerning, for example, best care processes [43,69], the interpretation of mammography images [28], the prediction of sepsis [45], fall detection [99], risk situations for patients with dementia [101], or treatment inefficiencies due to patients' lack of adherence [95]. ML involves also unsupervised methods that can be used to create medical taxonomies about the topics observed in online medical digital libraries [17] to help information retrieval by consumers. CBR was also used to retrieve hemodialysis cases with similar time series features, relying on Temporal Abstractions [65].

In other works, knowledge was acquired either from experts or users. In [34], a methodology is proposed to acquire health consumer terminology and align it to standard medical terminology. In [57], a method is introduced for formalizing eligibility criteria for breast cancer clinical trials. Wiki-driven methods were also used for specialists' self-acquisition of knowledge on sepsis protocols for monitoring and treatment [55]. Other examples were found on the construction of preliminary knowledge-bases to facilitate collaborative computerization of clinical guidelines [97], the composition of rules to combine comorbid treatments [59], or the capture of different expert interpretations of objects within breast radiograms and mammograms [21]. Specific tools may exist to support the elicitation of knowledge about, for instance, sophisticated triggering patterns for intelligent alerts [71] or quality indicators of care [52].

3.3.2. Knowledge specification

The most prevalent representation of clinical knowledge in the papers is by means of Computer-Interpretable Guidelines (CIGs) [102] (see also Section 3.2). Some papers focus on environments for acquiring and specifying CIGs; e.g., [49] presents the "Human Cli-Knowme" Project, an environment for building a universal, formal, procedural and declarative clinical knowledge base for the automation of therapy and research. In [71], the same group presents iALARM, a language for formalizing rules to trigger alerts in response to declarative patterns observed in patient data. Several environments were developed for the collaborative formalization of CIGs [97], thus Diaflux [54] is presented as a graphic language to develop CIGs and Meta-GLARE [76] as a meta-language to define CIG-based systems.

Clinical knowledge may not necessarily be expressed in the form of CIGs but in other different ways such as ontologies, rules, or ad hoc computer structures. Ontologies were used to map diagnostic and therapeutic procedures (e.g., [33,26]), to describe the handling of comorbid diseases [20], and to define patient self-management activities

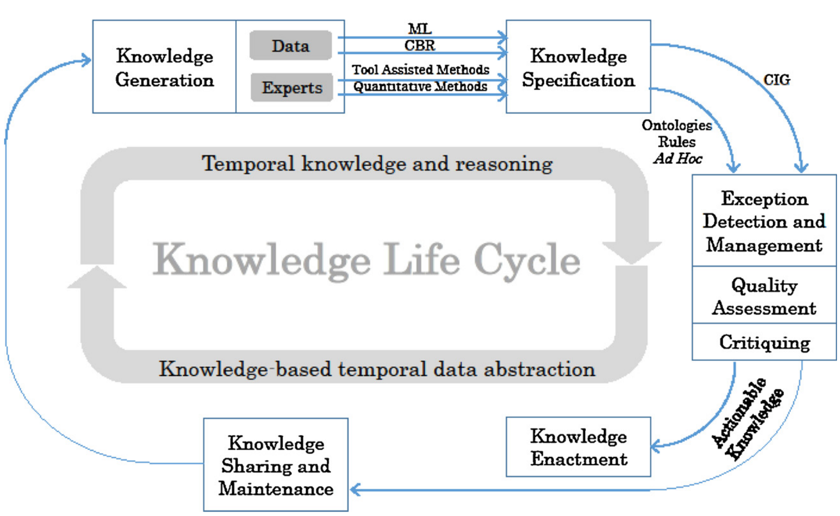

Fig. 2. Knowledge Life Cycle Processes detected in the analysis.

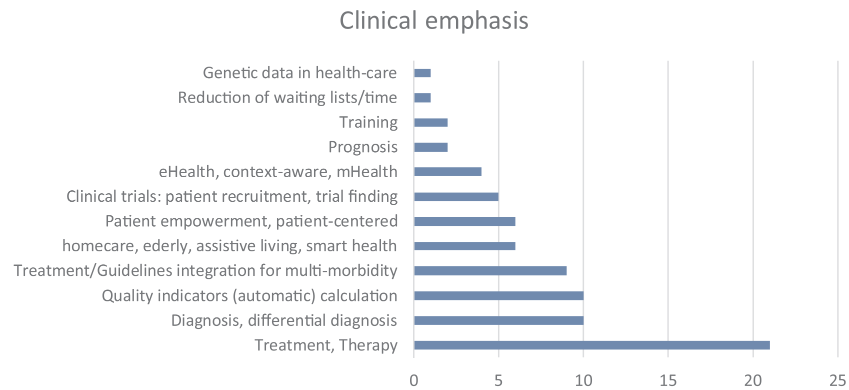

Fig. 3. Prevalence of the clinical emphasis of the papers in KR4HC.

[30]. In [59], rules were used to combine treatments for multi-morbidity, and in [19] clinical guideline expressions were encoded in GELLO. Authors in [57] defined patterns of eligibility criteria for clinical trials that cover most criteria found in clinical guidelines and [40] proposed a language to capture and synthesize the knowledge generated in such trials. Knowledge in clinical guidelines were also represented in first order logic [74] or combined under a mathematical model, in order to deal with comorbidity [72].

3.3.3. Exception detection and management, quality assessment and critiquing

Before clinical knowledge is applied, exceptions to the general rule must be considered. In addition, sensitive clinical knowledge must continually undergo quality analysis, critique, and review. In [52], SWRL rules were used to express guideline constraints and they were checked against CIGs that are personalized to the patient's context [60,63]. used continuous planning to adjust care pathways when deviations occur in the patient's expected state. [75,82,90] used Answer Set Programming to detect lack of adherence to clinical guidelines. In [96], the authors described a framework that can address multi-morbidity as well as exceptions. In [63], a method was developed for conformance checking that computes fitness of individual activities in the setting of sparse process execution information, i.e., not all activities of a patient's treatment are logged. In [52], the authors suggested calculating quality indicators using semantic queries in SPARQL that use SNOMED-CT codes.

3.3.4. Knowledge enactment

Among the papers, there are some in which new engines for the enactment of CIGs are described. The main approaches focus on adaptive continuous planning [51,60], a meta-engine for CIG execution [80], and the use of semantic-web inference rules in SPARQL [86, 87] for clinical guidelines application.

3.3.5. Temporal knowledge & reasoning, knowledge-based temporal data abstraction

Time receives a special consideration in medical knowledge representation and reasoning (see also Section 3.1). In [58], several computational architectures are described that aim at the management of temporal knowledge. In [70], CliniText uses temporal data abstractions for the intelligent summarization of longitudinal clinical records. iALARM, in [71], is an intelligent time-based alert language for activation, response, and monitoring of medical alerts. Paper [66] proposes temporal hierarchical planning techniques to handle exceptions arising during CIG enactment. In [82,91], it is acknowledged that the effects of the clinical actions have a probabilistic distribution in time, and that considering such probabilities further enhanced the support for interaction detection [93] represented temporal constraints in clinical guidelines using openEHR archetypes and Guideline Definition Language. Alternatively [36], captured the dynamics of clinical processes with temporal logic, and [39] the temporal uncertainty of clinical tasks with Possibility Theory. Some other papers described the abstraction of temporal knowledge from the analysis of time series [57] or temporal genomic data [92].

3.3.6. Knowledge sharing and maintenance

Knowledge sharing, reuse, and maintenance are outstanding actions within the knowledge lifecycle that pays off the effort usually involved in the process of formalizing clinical knowledge. In [19], Peleg allowed appropriateness criteria in CIGs to be shared using standards. In [81], Prolog rules were used to identify and maintain the grade of evidence of clinical recommendations. In addition, a search and filtering method was proposed to select the medical terms that appear in the conclusions of the guideline to generate a query to search for new evidences, for guideline update [85,88].

In summary, KR4HC papers cover the entire life cycle of knowledge generation and usage. Most papers address knowledge generation, exception handling and critiquing, followed by knowledge representation.

3.4. Clinical emphasis

The clinical emphasis of the papers is shown in Fig. 3. The most prevalent emphasis is on treatment (21 papers), followed by diagnosis (10), clinical indicators (10), and guideline integration for multi-morbidity patients (9).

It is evident that therapy is the most prevalent clinical emphasis, which is consistent with the large focus on clinical guidelines that tend to specify care processes for patients that have already been initially diagnoses with specific diseases.

3.5. Level of development

In order to analyze the level of maturity of the works described in the papers, we defined four maturity levels: formal, implementation, testing, and deployment. These are adapted from the respective technology readiness levels 1–2, 3–4, 5–7, 8–9 of the NASA's Technology Readiness Level framework, TRL9 [11]. TRL9 is a nine-level scale internationally used in the industrial sector to delimit the degree of maturity of a technology. Papers were each classified into one of these maturity levels depending on the information contained in their corresponding abstracts.

The formal level comprises those papers which describe basic principles, technology concepts, or application formulations, according to their abstracts. The implementation level refers to papers describing technologies, methods, prototypes, or systems already developed and validated in a controlled environment. The testing level corresponds to abstracts describing works that show a clear application in a real environment but not as part of the regular clinical activities of a health care center. Only if the paper reports on the professional application of a technology, a method or a system in daily clinical activities, it is considered that the work reaches the level of deployment.

Our study concluded that 11% of the abstracts reported no information on the level of development, 26 papers (22%) remained at the formal level (e.g., describing innovative clinical knowledge-based models), 60 abstracts (52%) described works about implementations, and only 15 (13%) described tested works. Apart of these, only 2% of the abstracts described works which involve real deployments.

This shows a clear bias of the works towards research and the innovation of ideas rather than the presentation of final products and their impact, which is in accordance with the nature of workshops in general. It can also be interpreted as a reflection of the incipient and promising incorporation of knowledge-based intelligent systems into the clinical sector [15].

3.6. Diseases

Whenever the title, the abstract, or the keywords of the papers mention concrete targeted diseases, these were stored for analysis. First, they were sorted according to the International Classification of Diseases (ICD-11) [12], and their heterogeneity studied. The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016) of the WHO on the incidence, prevalence, and percentage growth of diseases in the world [13] was used to determine the relevance of the diseases found.

Fifty-nine papers described AI technologies developed for or applied to 30 concrete medical issues or diseases, 34 of them (58%) were generic enough to be applicable to more than one disease. Using the ICD-11 classification, the most frequent uses were on cancer (37%), followed by diseases of the circulatory system (32%). As Fig. 4 shows, breast cancer was the most frequent single disease, followed by arterial hypertension and diabetes Mellitus. Other papers were focused on clinical issues such as chronicity (13.6%) or comorbidity (10.2%), which are considered extended X-codes in the ICD-11. Other less frequent diseases were also observed, these related to the respiratory system (e.g., chronic obstructive disease COPD, 6.8%), the circulatory system (e.g., atrial fibrillation, 6.8%), or the nervous system (e.g., transient ischemic attack, 5.1%). Some papers were centered on the cases observed in concrete medical services such as ICUs (6.8%), or radiology (3.4%).

When the list of diseases is compared with the diseases with a higher prevalence, incidence, and percentage growth between 2006 and 2016 [13], we observe that the five concrete cancers considered in the papers are among the most relevant neoplasms, but we found that there is a lack of studies on others equally important (e.g., liver cancer, malign skin melanoma, uterine cancer, or brain and nervous system cancers). A similar situation is observed for diabetes Mellitus which is the most prevalent of the endocrine diseases, COPD (with asthma, which is not found) for the diseases of the respiratory system, transient ischemic attack for cardiovascular diseases, or peptic-duodenal ulcers among the digestive diseases. Essential hypertension was not found in the study [13], but it is well recognized as one of the leading chronic diseases today. Atrial fibrillation was found in 4% of the papers, but its relevance in terms of incidence and prevalence is much lower than in other diseases of the circulatory system, such as ischemic heart disease or cerebrovascular disease, that were not found. From this viewpoint, there is a potential for the application of knowledge-based computerized approaches to diseases not yet considered, such as diseases of the immune system, mental, behavioral or neurological disorders, skin diseases, diseases of the musculoskeletal system, or conditions originated in the perinatal period, that affect large population groups [13]. Some of these diseases are more typical of third world areas (e.g., tuberculosis, infected tropical diseases, malaria, or nutritional diseases) and, therefore, their absence in the studies analyzed may be due to the natural tendency of the working groups to focus on diseases which are more frequent in closer health care centers. Other missing diseases that are frequent are more global (e.g., HIV / AIDS, common infectious diseases, Alzheimer's, or mental disorders).

3.7. Topic trends

The topics with a higher variability along the years (measured in terms of their respective standard deviation, SD) were those related with clinical practice guidelines as a source of knowledge, CPG modelling as a knowledge engineering process, and computer-interpretable guidelines (CIG) as the formal modelling languages to model clinical knowledge ($SD > 2.3$). These topics were present in several papers of different years. This variability should not be interpreted as an irregular interest in these highly related topics, but surely as a consequence of the costs of development that these topics involve, which hinders research groups from a continuous publication of relevant advances.

The number of papers related to medical treatment also showed a high variability along the years ($SD = 2.1$). The number of papers on ontologies, or those related to knowledge acquisition were also highly variable in different years ($SD = 1.8$).

We also identified some years with a special production of papers related to certain topics. For example, year 2011 was special at knowledge acquisition and knowledge representation for clinical treatment (91.7% of the papers). Similarly, year 2014 was intense in the

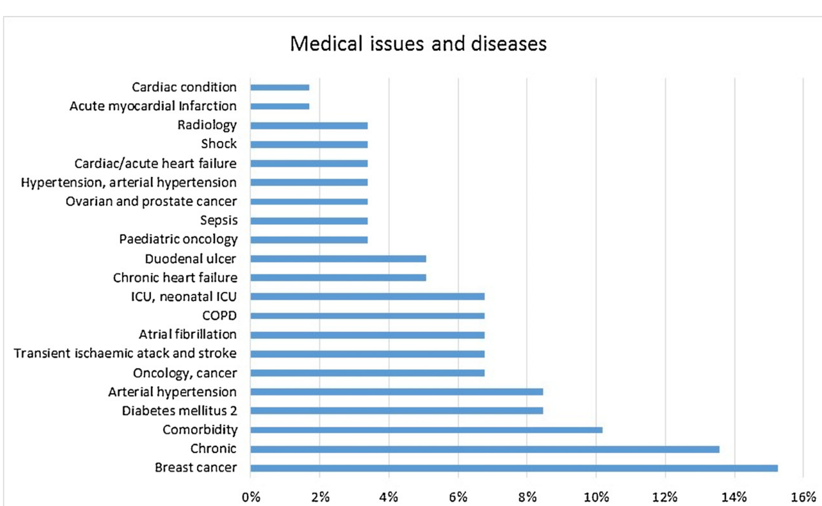

Fig. 4. Percentages of medical issues and diseases addressed in the papers in KR4HC.

number of papers related to clinical guidelines and CIGs, but also in guideline modelling (75% of the papers).

The timeline analysis of the number of publications related to each one of the 155 topics on knowledge representation for health care (see Appendix) that we identified gave rise to the detection of some trends. These must be taken cautiously and not necessarily representative of the whole field of knowledge representation for health care, but just as the evolution of the topics in the papers published in ten years of the workshop. Among these trends, it is worth outlining the following: clinical pathways and workflows and problems like adherence or compliance detection seem to lose weight since 2012, just like ontologies and guideline modelling, since 2014. On the contrary, topics like EHRs, CIGs and clinical decision support systems show a continuous interest along the years. Semantic terminologies such as OWL had a special production period in 2011-14, reaching 70% of their total production. Rules and logic are constantly used representation formalism, but Bayesian networks or Markov models are only sporadically used, probably because they are more specific purposed. Works on knowledge acquisition were more frequent in 2009-12, while knowledge production by machine learning or data analysis was more intensively addressed in 2016-18, but not exclusively. Knowledge integration and interoperability was observed in 2010–2013 papers, but then stopped, not because these issues were solved in the health care domain, but due to the discontinued participation in the workshop of groups with these work lines. Temporal knowledge was also present since 2012. Diagnostic problems were only addressed at the beginning of the period (before 2012), while therapeutic issues prolonged along the whole decade. This is much aligned with the reality of clinics, where diagnosis is more definitional and treatment more challenging. The concern for quality indicators is represented by the works published in the years 2011-16. We also observed that the maturity of the works that goes from pure theoretical approaches to full application in medical settings has not evolved during the decade 2009-18. However, the number of technologies and systems tested on public databases or taxonomies of terms was common in the first two years (67% of the cases), but completely disappeared after 2013. We found no sound rationale for this.

With regard to diseases, oncology issues are more present in the years 2009-11 (60% of all the publications) while the rest of diseases are uniformly distributed along the whole period.

Apart of the analysis of the papers in the KR4HC workshop, we also performed a search in Pubmed with query (((("knowledge representation") OR ontology OR CIG)) AND (healthcare OR "health care")) AND ("2009″[Date - Publication] : "2018″[Date - Publication]). From the 641 papers recovered, we selected 208 whose titles were related to our review topic. We downloaded the abstracts and made a quick search of the most frequent topics found in the KR4HC papers, then counted their frequencies. The most frequent topics in KR4HC turned out to be also very frequent in the Pubmed search.

3.8. Challenges of knowledge representation for health care

Knowledge representation in health care is a vast and complex area that tries to solve or help practitioners in multiple and diverse clinical issues. The evolution of this field can be either by developing new specific solutions to concrete clinical issues by means of the application (or adaptation) of current computer and artificial intelligence technologies to these problems, or alternatively by the incremental evolution (or integration) of technologies to solve the problem of knowledge representation in health care globally. In our analysis, we mainly found works that followed the first approach. However, during our analysis we could identify some relevant global aspects of knowledge representation in health care. Among them, we identified some ones that, according to our experience, represent ongoing or emerging challenges.

The integration of medical vocabularies, ontologies, CIGs and EHRs: clinical terminologies such as SNOMED-CT, ICD, or ICPD contain the basic building blocks to construct knowledge structures. The convergence of these terminologies towards a single coding system seems highly unrealistic, so final technologies to facilitate or automate interoperability will be needed. Ontologies are also powerful tools to represent knowledge about the semantic interrelations of the clinical concepts contained in these terminologies. The flexibility of ontologies to represent declarative knowledge and their ability for incremental growth make them a solid technology for continuous incorporation of knowledge and also to be adapted to new medical findings and paradigms such as patient-centered health care, precision medicine, or the incorporation of genetic and omics knowledge. Ontology languages and frameworks like Open Knowledge-base Connectivity (OKBC) and OWL, do not have detailed semantics to easily express procedural knowledge. CIGs and their languages can play this role for capturing the semantics of healthcare processes. The efficient integration of CIGs with Electronic Health Records and with standards like HL7 will be a condition for their future success.

Knowledge evolution and maintenance: CIG development and maintenance are difficult and time consuming. In addition, the great diversity of CIG languages divides the efforts of the community and hinders the advancement of this technology. An optimal tradeoff between ease of use and versatility of CIG languages to represent the great diversity of medical knowledge will be a determining factor for the hegemony of one CIG language in front of the rest. The ability to reach a commercial product and the capacity to reach a receptive clinical market will be also decisive in the process. In addition, it would be advisable for CIG languages to transform their knowledge structures into basic reasoning structures, such as formal logic, to take advantage of the many multifunctional capabilities and tools that have been developed for logic over the years.

With regard to the knowledge life cycle, we identified the following emerging challenges:

Knowledge summarization and tailoring for precision medicine: Tools for real-time access to health care knowledge at the point of care already exist. However, they could benefit from the development of new technologies for knowledge filtering. These should show or apply only the knowledge required for the clinical case under consideration, leaving aside the non-relevant knowledge. Precision and patient-centered medicine will also benefit from new supportive technologies to deal with multifaceted knowledge that comes from different disciplines.

Big-data analysis to support data-driven medicine: In the future, modules for knowledge elicitation from big data analysis will coexist with knowledge engineering approaches that transform the evidence-based knowledge of clinical guidelines into CIG structures. Methods to extract and ascertain causal relations and statistical significance within this data-driven generated knowledge will be needed and integrated together with CIG tools.

From a clinical perspective, some other challenges appear to be addressed with KR technology:

Multimorbidity: Multimorbidity is not only about drug-drug interaction detection, but also about the adaptation of treatments to the conditions of the patients, the consideration of risk factors, the combination of treatments for pluripathology patients, genetic medicine, and predictive medicine. To cope with this complexity, new technologies for the integration of clinical guideline, the merging of procedural knowledge and the design of medications have to evolve to reach an acceptable risk-free level.

Incorporation of genetic and omics knowledge in health care: The integration of phenotypic and genotypic knowledge is a pending task. Current works are focused on the analysis of omics data with machine learning technology to identify effective models that could predict phenotypic traits, clinical risks and outcomes, but also to produce biomarkers that could identify concrete pathologies. As new predictive models and biomarkers are identified, it will be necessary to represent this new kind of knowledge and relate it to the associated clinical knowledge available.

According to the progress of the field of KR in health care, the main challenges found are:

To facilitate the incorporation of knowledge-based technologies and systems in health care: Knowledge representation technology has a long tradition in health care, but its application in real clinical settings is scarce. A possible way to overcome this situation could be to establish standard, clear and efficient ways to facilitate knowledge-based technologies and systems, which are developed at the research level, to effectively progress towards final products applied in real clinical contexts.

Extend the utility of these technologies and systems: Some KR solutions to health care issues may not only be valid in the clinical contexts or diseases for which they were developed and tested, but their usefulness can be extended by assessing their validity to other diseases which they were not originally created for.

4. Conclusions

KR4HC is a stable community, still active after ten years. A persistent focus has been knowledge representation, with a focus on semantic-web ontologies and on clinical-guideline based decision-support. Two topics that are receiving growing attention are the integration of computer-interpretable guideline knowledge for management of multimorbidity patients as well as patient empowerment and patient-centered care. A topic receiving less attention is workflow management for healthcare processes. KR not only has a long tradition of application to health care problems, but currently faces promising new challenges such as supporting precision medicine and integrating both data-driven and clinical guidelines knowledge. It is interesting and gratifying to note that many of the methodologies proposed are generic enough to be applied to a variety of different disease domains. We hope that the KR4HC community will continue to make important contribution that are also generic to non-medical domains.

Declaration of Competing Interest

The authors declare there are not conflicts of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.artmed.2019.101713.

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