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REVIEW PAPER

A systematic review of technologies and standards used in the development of rule-based clinical decision support systems

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Abstract
A Clinical Decision Support System (CDSS) is a technology platform that uses medical knowledge with clinical data to provide customised advice for an individual patient's care. CDSSs use rules to encapsulate expert knowledge and rules engines to infer logic by evaluating rules according to a patient's specific information and related medical facts. However, CDSSs are by nature complex with a plethora of different technologies, standards and methods used to implement them and it can be difficult for practitioners to determine an appropriate solution for a specific scenario. This study's main goal is to provide a better understanding of different technical aspects of a CDSS, identify gaps in CDSS development and ultimately provide some guidelines to assist their translation into practice. We focus on issues related to knowledge representation including use of clinical ontologies, interoperability with EHRs, technology standards, CDSS architecture and mobile/cloud access. This study performs a systematic literature review of rule-based CDSSs that discuss the underlying technologies used and have evaluated clinical outcomes. From a search that yielded an initial set of 1731 papers, only 15 included an evaluation of clinical outcomes. This study has found that a large majority of papers did not include any form of evaluation and, for many that did include an evaluation, the methodology was not sufficiently rigorous to provide statistically significant results. From the 15 papers shortlisted, there were no RCT or quasi-experimental studies, only 6 used ontologies to represent domain knowledge, only 2 integrated with an EHR system, only 5 supported mobile use and only 3 used recognised healthcare technology standards (and all these were HL7 standards). Based on these findings, the paper provides some recommendations for future CDSS development.

Keywords Clinical Decision Support · Rules engines · Interoperability · Technology Standards · Ontologies

1 Introduction

Various definitions exist for a CDSS, for example, a CDSS is "*an active knowledge system that generates case specific advice, based on two or more items of patient data*" [1] or "*an active intelligent system capable of assisting the medical professionals by making specific recommendations and decisions based on the analysis of patient specific information and related medical facts*" [2]. From a system architecture perspective, a CDSS implementation as a diagnostic tool is essentially an expert system built to present helpful information and advice to the clinician/physician at the point-of-care. The main responsibilities of a CDSS are to support decision making, improve the overall patient quality of service and increase patient diagnostic and prognostic capabilities to the best available level, eliminate unnecessary mistakes and cost, and increase productivity [3]. The expanding medical knowledge, patient information, diagnostics, diseases and treatment methods, by necessity, is becoming a science of information [2].

Expert systems consist of two main parts: the knowledge base and rules, and the Inference Engine [4]. The Inference Engine evaluates given parameters with existing knowledge and rules to deduct new knowledge about a specific case and aid the clinician's decision-making process, usually at point-of-care. The inference mechanism (the mechanism that comes to a conclusion based on the knowledge base) can be achieved using a diverse range of techniques including but not limited to: Bayesian

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networks, neural networks, genetic algorithms, rule-based systems (expert systems), decision trees (logical conditions), casual probabilistic networks (statistical modeling), data mining, natural language processing, case-based reasoning, and supervised/unsupervised training [1].

The area of CDSSs can be confusing with a plethora of different technologies, standards and methods used to implement them. Thus, it can be difficult for practitioners to determine an appropriate solution for a specific scenario. This study's main goal is to allow an in-depth, better understanding of different technical aspects of a CDSS and ultimately provide some guidance to suitable solutions that should be of interest to software developers of CDSSs and also health practitioners involved in commissioning or development.

This study will perform a systematic literature review of the technologies used to develop rule-based CDSSs, focusing on papers that contain a clinical evaluation of the CDSS and discuss technical aspects of the implementation of the rules engine, including how knowledge has been represented and used. In addition, the paper examines the standards used to develop CDSSs and their integration/interoperability with Electronic Health Record (EHR) systems. The next section provides background information on CDSSs, the third section discusses the research questions this paper attempts to answer and the methodology used to review the literature and the fourth section discusses the findings. The final section provides conclusions and recommendations from the study.

2 Background

2.1 Clinical decision support

CDSSs fall under two main categories with regards to how they capture medical knowledge [5–7] that have different approaches on how to infer clinical knowledge (see Fig. 1):

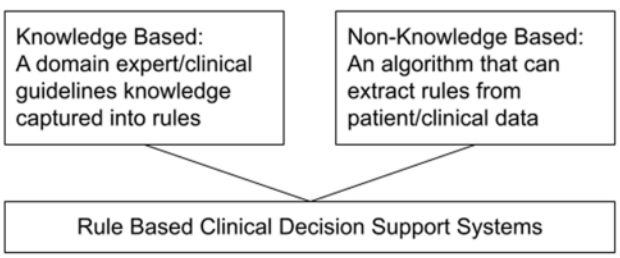

Fig. 1 Knowledge Capturing Approaches

- Knowledge Based

  Work-flow driven, use logical flows that contain statements referencing and manipulating medical data;
  Rule-based reasoning, capture knowledge in the form of IF–THEN statements and forward chaining, until a conclusion is reached;
  Probabilistic reasoning, use Bayesian networks and graphical representations that capture the relationship between disease and symptoms with conditional probabilities.

- Non-Knowledge Based

  Machine Learning (ML), learn or train on large datasets of clinical data.

  - Artificial Neural Networks
  - Genetic Algorithms
  - Support Vector Machines.

Knowledge-based systems, also known as expert systems or rule-based systems, use an extensive clinical knowledge base containing subject-specific knowledge taken from the medical literature, or from one or more experts. Non-knowledge based systems, also known as case-based systems, use machine learning (ML) to look for patterns in clinical assessment data to suggest a diagnostic probability. They are described as non-knowledge based, as the system does not actually have any knowledge prior to a ML algorithm process taking place.

Non-knowledge approaches are very important to the future of CDSSs as they simplify the knowledge acquisition and maintenance process, a process that is time consuming and requires considerable human effort [2]. This type of system will be more widely used in the future when "big data" applications are widely used in healthcare to provide potentially more accuracy in diagnosing disease than the average clinician [5]. The Watson Health system developed by IBM uses natural language processing and information mining tools to provide clinical guidance [8]. Although this type of system can solve complex decision-making problems, they require large sets of labeled data in order to train their algorithms and generally do not provide the rationale behind the decisions made [8]. A detailed survey of machine learning in CDSSs can be found in [9].

This literature review focuses on knowledge-based CDSSs and examples of such systems are discussed in the Analysis section. Knowledge-based CDSSs are composed of three basic architectural parts, namely the Medical Knowledge Base, the Electronic Health Record, and the Inference Mechanism (reasoning) [2], although the EHR may be a separate system. We briefly discuss these components below.

2.2 Electronic health record (EHR)

The EHR stores a collection of patient health data in a secure digital form. These records are shared through a network and include information such as medical history, allergies, immunization status, lab results, and personal statistics. The EHR should accurately capture the most up-to-date health status and history of a patient. Standards have been developed to define how EHR data should be structured, semantically described, and communicated. These standards include HL7 (v2, v3, and FHIR), openEHR, ASTM E1384, CEN's TC 251, and ISO TC 215. EHRs also often rely on medical terminologies such as SNOMED CT (SCT), LOINC, ICD, RxNorm, and UMLS. We discuss standards and terminologies in the following sections.

2.3 Clinical rules engines languages and standards

Rule-based systems are characterized by their high degree of agility to cater for constantly changing circumstances. Rule-based systems are made up from a rule-base (usually decomposed into rule-sets) and an inference engine that operates on the rules. Imperative for this system paradigm approach to work and be easier to maintain is that although the rules collectively should behave as part of the program, they should be stored as data [10].

One of the first CDSSs called MYCIN was developed in the early 1970s at the University of Stanford. Developers accepted that straightforward algorithms of statistical approaches were unsuitable for healthcare with the underlying knowledge not well understood and disagreement even between clinical experts on how best to treat a patient. The nature of these types of problems led the researchers to use interaction rules to capture knowledge about organisms that can cause infections and the antibiotics appropriate to treat them [5, 11].

Rule-based systems are used to develop CDSSs because of their flexibility and agility, an advantageous approach when working with clinical knowledge that is changing constantly with new discoveries from studies. Furthermore, clinicians are not always confident of the rules that should apply to a specific situation [11]. Rule-based systems essentially capture knowledge with conditions in logical systems, similar to first-order logic. The rule is specified in the form of IF–THEN clauses including logical functions and operations, and can be developed in various rule languages or formats [12].

There are now several rules engines that are used widely in diverse domains such as SEBASTIAN, Jess, Jena, CLIPS, OpenCDS, and iLog [13]. System for Evidence-Based Advice through Simultaneous Transaction with an Intelligent Agent across a Network (SEBASTIAN) is a CDSS framework that uses web services, with a write once use everywhere medical knowledge language. The SEBASTIAN framework also includes a rules engine. Jess is a Java-based rules engine that provides rule-based programming for expert systems based on the Rete algorithm for logic inference. Jess is a superset of the CLIPS object-oriented language for implementing expert systems. Jena, a semantic web framework for Java, can extract and write data to Resource Description Framework (RDF) graphs that represent an abstract model. Jena also supports the Web Ontology Language (OWL). OpenCDS is an open-source, standards-based framework that provides tools and resources to implement a CDSS. C Language Integrated Production System (CLIPS) is an object-oriented language that can be used to build expert systems. iLog is a business rules management system with a rule represented by a statement of logic that is used to make a business decision.

In CDSS, there are some major healthcare standards regarding Clinical Guideline Representation, Patient Information and Medical Terminology as identified in [13] that will be discussed in the following subsections.

2.3.1 Clinical guidelines

A key part of a CDSS is representing clinical knowledge. This subsection discusses the use of clinical guidelines to represent clinical knowledge. GLIF (Guideline Interchange Format) is a computer-interpretable guidelines (CIGs) language for modeling and executing clinical practice guidelines (CPGs). GLIF supports sharing of CIGs across different medical institutions and platforms. GLIF defines an ontology for representing guidelines, as well as a medical ontology for representing medical data and concepts. In GLIF3, guidelines can be encoded at three levels: a conceptual flowchart, a computable specification that can be verified for logical consistency and completeness, and an implementable specification for inclusion into particular organizational information systems [14].

NewGUIDE is a guideline representation formalism developed at the University of Pavia. In NewGUIDE the guideline is hierarchically structured in "pages" representing different abstraction levels: the first (high level) page is normally composed by a flowchart of non-atomic tasks, whose expansion is described in inner pages. The main features of NewGUIDE are: the capability to represent sequential, parallel and iterative paths, the possibility of running analytic-decision models when decisional tasks are not associated with specific rules, the use of a terminology server to define the guideline task names, and finally the possibility of generating a Petri net written in WPDL (Workflow Process Definition Language) for guideline simulation purposes [15].

SAGE clinical guidelines representation is a standards-based, shareable and interoperable active environment using HL7, medical terminologies (eg. LOINC, SNOMED) and

virtual medical record standards. Asbru is a task-specific and intention-based plan representation language to embody clinical guidelines and protocols as time-oriented skeletal plans. Skeletal plans provide a powerful way to reuse existing domain-specific procedural knowledge, while leaving room for execution-time flexibility to achieve particular goals. Proforma is a formal knowledge representation method for the development and execution of clinical guidelines. Proforma employs a process description language that is based on a logical model of decision making and plan enactment, the description language is a task-based formalism that uses plans, decisions, enquiries and actions. There are software suites of authoring, verification and testing tools and can support web or standalone execution [16].

2.3.2 Patient information

The HL7 Virtual Medical Record (vMR) v3 standard specifies a data model for representing clinical data relevant to a CDSS. The purpose of the vMR is to provide a simple and intuitive representation of data that can be used across CDSS implementations and to address the issues of interoperability between organizations and systems.

The HL7 Clinical Document Architecture (CDA) is an XML-based markup standard intended to specify the encoding, structure, and semantics of clinical documents for exchange. The HL7 Continuity of Care Document (CCD) specification, an XML-based markup standard intended to specify the encoding, structure, and semantics of a patient summary clinical document for exchange, is a constraint on the CDA standard. The HL7 Fast Healthcare Interoperability Resources (FHIR) is a standard data format that aims to simplify EHR-based data sharing. The FHIR standard is designed to address the technical (understanding the data) and semantic (exchanging the correct data) complexity for data exchange in eHealth.

Another interoperability standard is openEHR, an open specification in eHealth that describes the management, storage, retrieval and exchange of health data in EHRs, maintained by the openEHR Foundation. The atomic entity of openEHR is an archetype – a reusable data element and group definitions that can be reused in various clinical contexts, similar to a FHIR resource. However, FHIR does not require a specific language, whereas openEHR archetypes are designed using the Archetype Definition Language (ADL) [17].

2.3.3 Medical terminology

There are a number of standard medical terminologies used in CDSS systems including:

- Logical Observation Identifiers Names and Codes (LOINC), a universal standard for identifying medical laboratory observations and has expanded to include nursing diagnosis, outcomes classification, nursing interventions and patient care datasets.
- SNOMED Clinical Terms (CT), a collection of medical terminology that includes terms, codes, synonyms and definitions used in clinical documentation and reporting.
- The ICD (International Classification of Diseases, Tenth Revision, Clinical Modification), a system used by clinicians and other healthcare providers to classify and code all diagnoses, symptoms and procedures recorded in conjunction with hospital care in the U.S. It provides a level of detail that is necessary for diagnostic specificity and morbidity classification in the U.S.
- RxNorm, provides normalized names for clinical drugs and links its names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software. By providing links between these vocabularies, RxNorm can mediate messages between systems not using the same software and vocabulary.

2.4 Ontologies

The plethora of medical standards and the freedom to loosely follow each standard by vendors has resulted in the requirement for a common unified medical knowledge representation approach that will make integration and information exchange easier. In health informatics, ontologies offer a formal description of health-related domain information and provide a vocabulary for biomedical entities that address the unified medical knowledge representation problem [2, 18, 19]. Ontologies facilitate standardisation, flexibility for change, and therefore promote sharing and reusability of medical knowledge between CDSS systems implemented in different technology and standards [2, 20].

An ontology is part of artificial intelligence that focuses on conceptualizations of objects / knowledge. It encompasses a "*representation, formal naming, and definition of the categories, properties, and relations between the concepts, data, and entities that substantiate one, many, or all domains*" [21]. Ontologies generally appear as a taxonomical tree of conceptualizations, from very general and domain-independent at the top levels to increasingly domain-specific further down the hierarchy and they construct a vocabulary that represents knowledge by classifying and verifying terminologies [22]. As a domain-independent knowledge representation, an ontology is flexible and dynamic in expanding, managing and integrating knowledge from different sources as well as adapting it to the user's needs and allows easier knowledge sharing between domain applications. However,

there is a large number of ontological languages, which poses a challenge for ontological editors when integrating different ontological languages. It may also be difficult to turn specialist knowledge into an ontology particularly when the knowledge including its relationships are not clearly understood/defined or open to contradictions and misinterpretations or if there is a lack of agreement about synonymy when representing knowledge [23].

Ontologies are used in CDSSs to express complex structures and objects with complicated interconnections and still maintain flexibility and compatibility with other systems. Semantic reasoners are software that provide a higher level of abstraction from the ontology layer and can infer logical outcomes from a set of axioms. Thus, the inference engine usually relies on rules that are expressed in an ontology language. Although ontologies can be time consuming to develop they provide key support for exchange of information.

Amongst many ontology languages, the most commonly used ones are RDF, RDF Schema, OIL, DAML + OIL and OWL (OWL, OWL-DL, OWL Lite) with the main difference between them being the level of control on every concept.

OWL extends RDF to allow more complex relationships between RDF classes and provide more precise constraints. An ontology could be created without using an editor, however, there are ontology editors such as Protégé and Ontoterm that provide an interface and visualiser for non-technical users. A review of semantic web and rule-based inference engines is conducted in [12, 24, 25] and some prototypes have been developed to enable easier knowledge and rule capturing (eg. [18]). Clinical knowledge can be inferred using established rule languages such as RuleML and SWRL.

There are existing medical ontologies available online such as SNOMED CT and LOINC, and there are also ontologies that are domain-specific, for example, in diabetes, there is Diabetes Mellitus Treatment Ontology (DMTO), for cardiovascular there is Cardiovascular Disease Ontology (CVDO) and for stroke there is Stroke Ontology (STO-DRAFT/CVAO).

3 Research methodology

3.1 Research questions

In this work the focus is on rule-based CDSSs and the aim is to answer the following research questions using a systematic review of the literature:

1. How have the rules-based CDSSs been evaluated in terms of clinical outcomes?
2. What architectures, technologies and standards have been used to develop rules-based CDSSs?
3. Have the CDSSs been integrated with the organizational EHR?
4. How has knowledge been represented in rules-based CDSSs?

These research questions are designed to help capture theoretical aspects of CDSSs technologies and standards and the extent to which they are used in implementations of CDSSs, i.e. trying to identify evidence of gaps in theory and practice. For this reason this study only includes papers on CDSSs that discuss the underlying technologies used, how knowledge has been represented, and have been evaluated.

3.2 Systematic literature review

A systematic literature review of the most relevant databases with the following search terms was performed (adjusted to each database's querying method):

("Clinical Decision Support" OR "Diagnostic Decision Support" OR "e-health") AND ("rules engine" OR "inference engine" OR
"calculator" OR "business rule" OR "rule based")

The search was limited to the time period 2007–2019 in seven of the most relevant research databases, namely: Science Direct, Association Computing Machinery (ACM) digital library, Springer, BioMed, PubMed, Emerald, and Institute of Electrical and Electronics Engineering (IEEE) Explore. The application of the search terms on each of these databases yielded 1731 results (see Table 1) and by looking at the title, abstract, and a quick overview of the paper to ensure it discussed technical aspects of the implementation of the CDSS, including how knowledge had been represented and used, this reduced the total to 341 possibly relevant papers (see Fig. 2 for selection process). A thorough review of the 341 possible relevant articles was then further reduced to 114 relevant papers that were then further filtered to 15 works that included some form of rigorous evaluation

Table 1 Search Results by Database

Database	Search Results	Relevant Papers	Selected Papers
IEEE	20	16	0
ACM	19	11	0
BioMed	101	40	1
PubMed	68	29	1
Springer	1455	207	10
Science Direct	52	33	3
Emerald	16	5	0
Total	1731	341	15

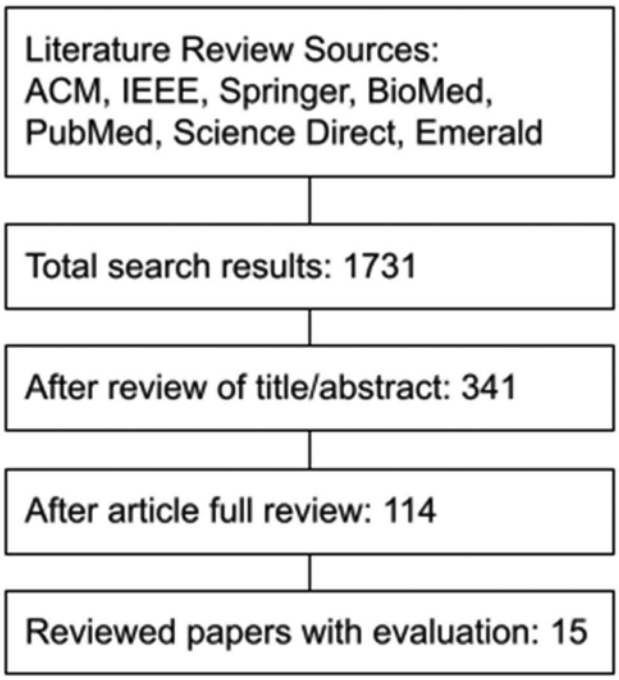

Fig. 2 Literature Survey Selection Process

of the system. This study is based upon those 15 papers (see Table 1 for breakdown of results by database).

Springer had the most results because the search terms could not be applied to the title and abstract only and the search returned papers that had the search terms present on the full text. The number of relevant papers seems more pertinent for Springer once the filtering and review processes were finished.

The papers were distributed between 5 reviewers. The reviewers were given a list of rules as inclusion criteria and the relevant information that should be extracted from the paper, if present. Inclusion criteria included all papers that used a rule-based approach in the health domain, including studies and reviews. Some of the information to be extracted was the medical area of the work, how the logic was integrated in the tool/study, how the Knowledge was represented and acquired, functionality of the used technology, system architecture, platform security and privacy and relevant accreditation, validation and evaluation of the study, hard coded logic, using an existing engine rule engine, rules engine language, logic editor. This information helped to form a useful and comprehensive view of the field of rules engines in the CDSS domain that to the best of knowledge of the authors has not been done before to this extent.

3.3 Inter-rater reliability

Inter-rater reliability (IRR) was performed and computed using Krippendorff's alpha, a well-regarded, flexible measure that accounts for chance agreements [26]. The IRR was measured on a subset of the papers found, five papers from each reviewer were selected at random to be reviewed by others. Based on the 5 reviewers, 25 papers and 95 decisions, a Krippendorff's alpha of 0.742 was computed which can be accepted as satisfactory [27]. The average pairwise agreement was 78.7%.

4 Analysis

This section addresses each of the research questions set out above based on the 15 papers that matched the original criteria. The subsequent section discusses the overall findings from the systematic literature review.

4.1 Evaluation

This section addresses RQ1: *How have the rules-based CDSSs been evaluated in terms of clinical outcomes?* 15 papers were found that evaluated clinical outcomes covering a range of medical areas including diabetes, cardiovascular, respiratory, drug use, paediatrics, triage, health examinations, intensive care, poisoning diagnosis, hepatitis, peripheral neuropathy, and lab tests.

4.1.1 Diabetes

There were three papers that covered diabetes [19, 28, 29]. Sherimon & Krishnan [19] discussed OntoDiabetic, an ontology-based CDSS to assess risk factors and provide appropriate treatment suggestions for diabetic patients. To evaluate the system, a case study was conducted with 250 patients with risk of overt cardiovascular disease (CVD), diabetic nephropathy and hypertension in primary health centres in Oman. Risk assessment of the diabetic patients in five different parameters (smoking, alcohol, physical, sexual and cardiac) was conducted using OntoDiabetic and compared with manual risk assessment by clinicians. Of the 250 patients, 123 were general diabetic patients having fewer complications and the risk of these 123 patients was on average 74% efficient in risk assessment. The remaining 127 patients had one of three complications, overt CVD, diabetic nephropathy and hypertension. 52 patients with overt CVD were assessed with 83% accuracy; 34 diabetic nephropathy cases were 79% accurate and 41 patients with hypertension were diagnosed by the system with 85% accuracy.

Hussain et al. [28] discussed the development of a cloud-based CDSS using a range of diverse inputs, such as sensors, user profile information, social media, clinical knowledge bases, and medical experts to generate standards-based personalized recommendations for diabetes. Input was converted into a standard interface following HL7 vMR

standards and submitted to the CDSS to generate recommendations. The system was evaluated with test data from 100 patients at Saint Mary's Hospital in Korea: 20 with type-1 diabetes, 40 with type-2 diabetes mellitus, and 40 with suspicions for diabetes but no specific diagnosis. The system generally performed well with three patients identified as suspicious for type-1 diabetes, who had not been diagnosed with diabetes. Two patients diagnosed with type-1 diabetes were placed in the type-2 category, although this was due to the patients having comorbidities that were not handled in the MLMs (Medical Logic Modules).

Serhani et al. [29] proposed an adaptive CDSS for patients with diabetes linked to an intelligent continuous monitoring scheme that handled semi continuous data streams from smart sensors monitoring blood sugar (BS) and blood pressure (BP). The system was evaluated using 13,650 readings related to BS and BP for 70 patients over a period of 6 months. The system was able to provide advice on lifestyle and exercise, food intake and medication based on different combinations of BS and BP readings.

4.1.2 Other clinical domains

The remaining selected papers were for a range of different clinical domains. Sorenson et al. [30] discussed the use of a frame-based knowledge representation to construct a bedside CDSS for ventilator weaning. The validation consisted of comparing the CDSS protocol with that of the paper-based system. A set of more than 2,000 recommendations were generated for every possible combination of variable values from the Acute Respiratory Distress Syndrome Network ventilation and oxygenation protocols for maintenance of mechanical ventilation. All were reviewed by a physician and respiratory therapist familiar with the protocols. Separately, the testing and clinical implementation of the weaning protocol was successfully tested with eight patients. 178 instructions were generated by the system and 80% of these were accepted by the clinicians and many of the rejections were mainly unavoidable. The computerized weaning protocol was subsequently integrated into the clinical environment.

The mobile CDSS GenSupport for congenital clubfoot treatment [3] supported the registration of patient information, supervised the treatment process, and provided advice during treatment. For the clinical evaluation of the CDSS, a dataset containing full treatment history of 17 patients with congenital clubfoot was used. The system provided the same treatment recommendations as performed by the clinician on 5 of the 17 patients. For the other patients, the system advised performing a tenotomy either before (7 of 17) or after (5 of 17) it was actually performed by the clinician. With the 7 cases, tenotomy was not performed according to the recommendations from the Ponseti expert group and the clinicians provided a sub-optimal treatment. With the 5 cases, the clinicians performed tenotomy earlier than the CDSS recommended and the clinicians' actions were most likely based on factors not documented in the patient data available in the evaluation.

Kumar et al. [31] proposed a hybrid approach of case-based reasoning (CBR) and rule-based reasoning (RBR) to build a CDSS for ICU, as an alternative to a purely rule-based system. The CDSS was developed by taking a CBR system and augmenting it with RBR functionality. The system was evaluated with real data from six ICU domains from a hospital in India, populated with five tagged cases that were very close to an old patient case. The relevance of the retrieved cases given a test case where retrieval effectiveness was defined in terms of precision and recall rates was examined. Similar results were obtained for all the domains with a maximum precision of 0.85, recall of 0.62, optimum threshold of 0.335 and k of 0.25, demonstrating the efficacy of the proposed approach.

Batista-Navarro et al. [32] developed a CDSS to provide timely information to clinicians about poisoning. The CDSS accepted signs and symptoms observed from a patient as input and presented a list of possible poisoning types with the corresponding management procedures that may be considered in making the final diagnosis. The CDSS was validated using 50 test cases, each test case consisting of patient symptoms and the expected poisoning type. The symptoms for each test case were entered into the CDSS and 96% of these cases were given the expected result.

Kunhimangalam et al. [33] aimed to show that fuzzy CDSSs for peripheral neuropathy improve diagnostic and predictive medical opinions. To evaluate the fuzzy CDSS, 104 NCS (Nerve Conduction Studies) data from Kannur Medical College in India were tested with normal cases and different peripheral neuropathy cases. Comparing the fuzzy CDSS output with that of a domain expert, the CDSS showed an accuracy of 93.26%.

Zhang et al. [34] developed a knowledge translation platform as part of a CDSS in DaYi hospital in China in 2013. As part of the evaluation, a case study related to medication prescribing was tested. During a 13-month period, 9,596 alerts were detected from 2,667,016 medical orders and 8,609 (89.7%) of the alerts were revised by physicians demonstrating observable behaviour change. The authors concluded that the knowledge translation platform successfully assisted in translating evidence-based rules into observable clinician behaviour changes.

Zhang et al. [35] developed a CDSS that supported the sharing of knowledge among heterogeneous healthcare information systems. The knowledge base consisted of independent and reusable knowledge modules (KMs) to meet core CDSS needs. A semantic web service framework was developed to identify, access, and leverage these KMs across

CDSS applications and care settings. The system was validated with two distinct CDSS applications at different hospitals in China: a clinical pathway management system with 298 patients and a mobile-based emergency triage system for trauma care in mass casualty incidents with 148 patients. For both cases, the knowledge base was instantiated with relevant domain knowledge mainly from standard CPGs and real patient data from the collaborating hospitals. Domain experts performed each CDSS task in two modes, i.e., using their own expertise and using the CDSS and the CDSS had an overall accuracy of 98.66% and completeness of 96.98%.

Karim et al. [36] developed a Belief Rule-Based Expert System (BRBES) that can suspect bronchiolitis under uncertainty with increased accuracy. To demonstrate the applicability of the system, data on the signs and symptoms of 200 patients with bronchiolitis (runny nose, fever, feeding, respiratory distress and wheezing) was collected from a hospital in Bangladesh. The diagnosis of the BRBES system was compared with that of an expert and was found to be more reliable based on pathology.

The UbiTriagem CDSS for triage based on web semantics and ubiquitous computing [37] was evaluated using 30 scenarios that already had a correctly documented triage. The automatic triage assessment from UbiTriagem was correct in 93.3% of the cases and, after adjustments in the underlying model, in 100% of the cases.

Mohammadhassanzadeh et al. [38] implemented a CDSS with plausible reasoning mechanisms that applied patterns from human thought processes, such as generalization, similarity and interpolation. The authors investigated the efficiency of the CDSS loaded with a hepatitis dataset dealing with different degrees of missing data using two metrics: (i) Coverage—the ratio of the number of answered queries (either correct or incorrect) to the total number of queries and (ii) Correctness – the percentage of answered queries that were correct. A medical expert used the CDSS to diagnose the possibility of survival for each patient. For each incomplete justification (i.e., for which the system has no answer), inductive and analogical reasoning was applied to supplement deductive reasoning with plausible inferences. Using their best judgment and medical experience, the medical expert then confirmed or refuted the justifications. The results showed that plausibly inferred knowledge extended the coverage of the knowledge base by, on average, 2%, 7%, 12%, and 16% for datasets with, respectively, 5%, 10%, 15%, and 20% of missing values. The authors posit that this expansion in the knowledge base coverage allowed complex disease diagnostic queries to be solved that were previously unresolvable, without losing the correctness of the answers.

Kopanitsa & Semenov [39] developed a first order predicates-based CDSS to analyze laboratory test results and deliver reports in natural language to patients. To evaluate the accuracy of the system, 1,000 randomly generated reports were created in a way that allowed validation of all 89 decision support algorithms. The reports were given to two pathology experts to review independently and the experts only disagreed with two reports. The decision support system has been implemented in the Helix laboratory service in Saint-Petersburg, Russia and was in commercial production in 2018 generating about 20,000 reports a day.

Kuo & Fuh [40] created a CDSS (HEALS) to assist clinicians to improve the quality of health examinations. To evaluate the effectiveness of the system, eight residents of a Taiwanese hospital with less than two years of clinical experience were given a set of relevant questions with four to seven possible answers divided into three levels of correctness — completely correct, partially correct, and least correct. For each question, to reduce bias only one or two answers qualified as completely correct and the others as partially correct or least correct. Two senior physicians with more than 10 years experience in health examination validated the questions/answers. An 18% improvement was achieved using the HEALS CDSS.

4.2 CDSS architectures, technologies and standards

This section addresses RQ2: *What architectures, technologies and standards have been used to develop rules-based CDSSs*? and RQ3: *Have the CDSSs been integrated with the organizational EHR*?

4.2.1 CDSS architectures

Velickovski et al. [7] identified different software architectural models used in CDSSs. The main factors that contribute to the selection of a model are the time and resources available, the level of integration with other health systems, and level and ease of reuse of software components. According to the study, there are four different architectural models with similar technology characteristics to develop a CDSS:

- The Standalone Model, no integration to an external Health Information System (HIS) or EHR;
- The Integrated Model, CDSS is tightly coupled to the HIS or EHR;
- The Standard-Based Model, CDSS is separated from the HIS/EHR and interoperability is achieved through the use of computer-interpretable guidelines (CIGs);
- The Service-Oriented Model, again the CDSS is separated from the HIS/EHR, but is integrated using service-based interfaces. The interfaces encode the clinical data and recommendations using ontologies and vocabularies. Here, standardization is based on the data transferred between the HIS and CDSS instead of the clinical rules executed by the CDSS as in standard-based systems.

Due to the growing support for mHealth, we were also particularly interested in CDSS support for mobile/handheld devices and use of the cloud. The majority of papers were Standalone, however, five were Service-Oriented [28, 34, 35, 37, 38]. In addition, five of the selected papers supported mobile/handheld device access [3, 28, 29, 35, 37]. Only one used the cloud [28].

4.2.2 CDSS technologies

A range of rules/inference engines were used in the selected papers. Some researchers developed their own engines [30, 31, 33, 36, 38, 39]. Other researchers used existing technologies; for example:

- The reasoning engine Pellet was used by [35, 37].
- An inference engine based on ANTLR (ANother Tool for Language Recognition) was used to develop a CDSS rules engine for drug use [34].
- The Eval3RulesEngine developed for mobiles based on the external library Eval3 was used by [3].
- Jess, a rule engine and scripting environment written entirely in Java, was used by [29]. Rules were specified using Common LISP (CLISP) type syntax and readings are inferred using Jess engine to generate advice for diabetes.
- HL7 Arden syntax was used to develop the rules for a cloud-based CDSS for diabetes [28]. Each diabetes rule was represented as an individual MLM and converted into a compiled C# class for execution by the Knowledge Inference Engine. Each MLM had a counterpart C# class.
- CLIPS (C Language Integrated Production System), a rule-based programming language for creating expert systems, was used to develop a CDSS rules engine for poisoning diagnosis [32].

4.2.3 CDSS standards

Only a small number of papers adopted standards and these tended to be HL7 standards:

- HL7 Arden Syntax, a formalism for clinical knowledge representation, and HL7 GELLO, to build queries to extract and manipulate data from medical data, was used to build a cloud-based CDSS for diabetes [28].
- HL7 InfoButton, a standard mechanism for CDSSs to request context-specific clinical knowledge from online resources, was used for the drug use CDSS [34].
- HL7 vMR (Virtual Medical Record) is a data model for representing the data that is analyzed and/or produced by a CDSS engine. HL7 vMR was used by [35] for their shareable CDSS system and for the cloud-based CDSS for diabetes [28].
- HL7 CDA (Clinical Document Architecture), an exchange model for clinical documents, was used by [28].

Surprisingly, no papers used HL7 FHIR.

4.2.4 EHR integration

This subsection addresses RQ3: *Have the CDSSs been integrated with the organizational EHR?* Without having to duplicate patient data, which can lead to errors, ideally CDSSs should be integrated with an EHR system. However, only 2 of the selected papers were integrated with an EHR:

- The cloud-based CDSS for diabetes [28] was integrated with the EHR at St Mary's Hospital in Korea by converting data from HL7 CDA to HL7 vMR format using the adapter interoperability engine (ARIEN).
- The CDSS to check drug prescribing [34] was integrated with the EHR at DaYi Hospital in China.

4.3 CDSS knowledge representation

This subsection addresses RQ4: *How has knowledge been represented in rules-based CDSSs?* From the papers identified, clinical knowledge representation were implemented in a range of ways. Ontology was the most common knowledge representation method identified in 6 of the selected papers. An ontology is normally used to represent:

- Domain knowledge including diagnostic knowledge that defines diagnostic rules and/or drug use rules [19, 28, 34, 35, 37, 38]
- Clinical guidelines including recommended care protocols for clinical problems [19, 34, 37, 38]
- Patient semantic profile including patient details entered by patients or clinicians [19, 28, 35, 38] and patient activities [28].

From the papers identified, no papers used existing ontologies such as those listed in the Background section earlier and instead created bespoke ontologies to represent the knowledge they required. Zhang et al. [34] developed a unified ontology containing diagnostic knowledge, treatment knowledge and pharmaceutical knowledge. [38] used an ontology to represent patient data in different formats and databases, explicit medical knowledge (available texts, journals, and clinical guidelines) and tacit medical knowledge and experiences of domain experts. Kuo and Fuh [40] created a custom health examination ontology to represent health examination data such as physical examination results and lab data. Sherimon and Krishnan [19] developed the *Diabetic Patient Clinical Analysis Ontology* to represent all the information required to analyze patient information, compute risk scores and suggest

treatment procedures according to given clinical guidelines. Hussain et al. [28] used an ontology to represent data from sensors and information retrieved from social media, activity history, user profile information, clinical data, expert knowledge, and expert recommendations. The Knowledge Repository also contained clinical information using HL7 Arden Syntax. Wunsch et al. [37] created a custom ontology based on the Manchester Triage System protocol and Zhang et al. [35] created custom ontologies of real-time patient data and semantic domain knowledge base containing static CDSS knowledge and executable CDSS rules.

OWL was the most used ontology language identified in this study [19, 28, 35, 37, 38] while one paper did not explicitly specify what ontology language was used [34]. Protégé was used by [35, 37] to create their ontologies and Arden syntax was used by [28] to represent expert knowledge and recommendations.

In terms of knowledge repository, a range of technologies were used. Hussain et al. [28] used Windows Azure and SQL Azure while Wunch et al. [37] and Kuo and Fuh [40] used a MySQL database. Zhang et al. [34] employed Microsoft's Entity Framework to generate a knowledge base schema from an ontology model, which was then stored in a SQL server database. When parsing the ontologies, Wunch et al. [37] and Kuo and Fuh [40] created a custom module written in Java and Zhang et al. [35] used Apache Jena while the other papers did not provide specific details, which may indicate the parsing was part of their bespoke inference engine.

Apart from the use of ontologies, XML and Common LISP (CLISP) were also used for knowledge representation. Chen and Skjelvik [3] represented the guidelines for clubfoot treatment in a decision tree implemented in XML. Kumar et al. [31] used XML as their rule base format. Serhani et al. [29] used CLISP to implement their rules for Jess inference engine.

Other methods were also used for knowledge representation. Kunhimangalam et al. [33] implemented knowledge as fuzzy rules. Karim et al. [36] used knowledge representation based around fuzzy logic to represent different types of uncertain data related to the signs and symptoms of bronchiolitis, which was then converted into conventional IF–THEN rules. Batista-Navarro et al. [32] adopted knowledge from Algorithms of Common Poisonings Part 1 and represented the knowledge as rules stored as CLIPS files in the file system. Kopanitsa and Semenov [39] developed a knowledge representation language based on the first order predicate logic. Sorenson et al. [30] used a frame to represent knowledge where a frame included a list of findings necessary to make a decision or carry out an action, and a logic or mathematical statement to determine its output.

5 Discussion

5.1 Evaluation

Addressing RQ1: *How have the rules-based CDSSs been evaluated in terms of clinical outcomes*? One of the key criteria for the selected papers in this review was that they had to contain an evaluation of clinical outcomes. No RCT or quasi-experimental studies were identified and many of the papers only contained small-scale evaluations. No papers examined the costs of system implementation or carried out any form of cost/benefit analysis.

In terms of clinical outcomes, some papers used real-time patient data while others used test data, either based on existing patient data, published test datasets or randomly generated data. Surprisingly many of the patient studies were relatively small. The largest study was for the OntoDiabetic CDSS [19], which was evaluated with 250 patients with risk of CVD, diabetic nephropathy and hypertension. Other real-time patient studies included the cloud-based CDSS [28] that was evaluated with test data from 100 patients: 20 with type-1 diabetes, 40 with type-2 diabetes mellitus, and 40 with suspicions for diabetes but no specific diagnosis; the adaptive CDSS for patients with diabetes linked to an intelligent continuous monitoring scheme [29] evaluated using 13,650 readings related to BS and BP for 70 patients over a period of 6 months; and the frame-based CDSS for ventilator weaning [30] was evaluated with eight patients.

Studies that used test patient data for evaluation included the belief rule-based CDSS for bronchiolitis [36] which used data from 200 patients with bronchiolitis and compared with that of an expert; the fuzzy CDSS for diagnostic and predictive medical opinions, which used a dataset of 104 nerve studies and the output compared with that of a domain expert; the CDSS for poisoning diagnosis [32] which used 50 test cases, each test case consisting of patient symptoms and the expected poisoning type; the mobile CDSS for congenital clubfoot treatment [3] which used a dataset containing treatment history of 17 patients with congenital clubfoot; the CDSS for ICU that adopted CBR and RBR [31], which used real data from six ICU domains using five tagged cases that were very close to an old patient case; and the CDSS using plausible reasoning mechanisms [38], which used a hepatitis dataset dealing with different degrees of missing data, although no indication was given on the size of the dataset.

Other studies used other datasets including the knowledge translation platform for medication prescribing [34], which examined the number of alerts raised by the system and how many prescriptions were modified based on the alert; the UbiTriagem CDSS for triage [37], which used 30

scenarios that already had a correctly documented triage; and the CDSS to analyze laboratory test results [39], which randomly generated 1,000 reports and asked two pathology experts to independently verify the reports.

5.2 CDSS standards

Addressing RQ2: *What architectures, technologies and standards have been used to develop rules-based CDSSs*? In terms of architectures, while there are various models proposed the majority of papers were Standalone and only five were Service-Oriented. None of the included papers used the Integrated or Standards-based model. Standards are very important in the development of systems generally and can lead to faster development times, enhanced reliability, enhanced security and can result in safer software. In particular, despite three decades of development CDSSs still suffer from interoperability issues. Many CDSSs exist as standalone systems or as systems that cannot communicate effectively with other systems [41]. Interoperability standards, such as FHIR, are continuously being developed and improved. These standards are already being utilized in commercial EHR systems and government agencies and medical organizations are supporting and some even mandating the use of these interoperability standards in health systems [42].

From the review it is clear that health standards are not widely adopted, with the exception of HL7. Only 3 of the 15 selected papers used recognised CDSS standards [28, 34, 35]. All the standards used were from HL7 including Arden, GELLO, InfoButton, vMR and CDA. None of the selected papers used FHIR or openEHR. This lack of use of interoperability supports the view of other researchers (eg. [41]).

The cloud also offers a solution to interoperability and cloud systems tend to conform to an open architecture, newer standards, and more flexible connectivity to other systems. Only one of the 15 selected papers [28] used the cloud.

5.3 Mobile

It is argued that mHealth is changing the way healthcare can be delivered beyond the use of apps for medicine, health and fitness and well-being of patients to use of remote monitoring and consultation, telemedicine and patient management and in our case clinical decision support. This change is driven by increased mobile device penetration and capabilities along with growing clinician and patient demand [48]. A mHealth-based CDSS offers the potential to reduce medical errors and improve the quality and efficiency of healthcare [49]. Several exploratory studies have been conducted on the use of mobile devices to deliver eHealth content and some had positive outcomes. But one of the issues with this approach is that the majority of mobile applications on Google Play and the Apple Store are not following any health guidelines and are usually not evidence based [50]. A review in 2014 suggested actual application of such systems to date has been limited [51]. We were interested to determine whether the landscape had changed and more mobile CDSSs were being developed and more evidence of their usefulness was available. In this review, 5 of the 15 selected papers supported mobile/handheld device access ([3, 28, 29, 35, 37]) and, as noted previously, none of these evaluations used RCT or quasi-experimental methodologies so like the 2014 review, evidence remains limited.

5.4 EHR integration

Addressing RQ3: *Have the CDSSs been integrated with the organizational EHR*? CDSSs that have been integrated into EHR platforms have been shown to enhance the quality of clinical care and improve patient outcomes and their acceptance by clinicians can be significantly improved if they are well integrated with the EHRs [43–46]. The integration of these systems also allows previous patient data to be accessed by the CDSS for its own inferencing needs and to save any data the CDSS may generate to be saved back into the EHR. This helps in avoiding redundant data entry and errors due to missing or incorrect data being entered. The integration between the two systems also has several other advantages such as single log on and consistent user interfaces [47]. Despite these benefits, only 2 of the 15 selected papers developed a CDSS that integrated with an EHR.

5.5 Knowledge representation

Addressing RQ4: *How has knowledge been represented in rules-based CDSSs*? Although the use of ontologies has been identified to have the potential to improve flexibility and reusability of knowledge, only 6 papers in the review actually used an ontology and others used alternatives such as XML,, CLISP, HL7 vMR format and first order predicate logic. There is no clear justification in the papers discussed as to why such an approach was taken, however, perhaps the knowledge to be stored was sufficiently simple that an ontology was not needed. There is also no clear justification on why creating a bespoke ontology to fit the domain was preferred compared to using existing ontologies. Our assumption is the choice may be due to personal preference by the programmers or knowledge engineers. Knowledge representation using OWL was the most commonly used ontology language identified in this study while Prot´eg´e was the only ontology editor used by the studies for its user-friendly capabilities in creating and visualizing ontologies. To store the knowledge, relational databases such as MySQL and SQL Server are commonly used for its security compared to XML. When parsing ontologies, the papers indicated the most common approach was to hardcode it into the CDSS followed by creating a custom module usually written in Java and using Apache Jena.

6 Conclusions

Rule-based systems are extensively used in CDSSs possibly due to the flexibility they offer for a system that is under constant change. The increase in generated information, together with the increase in evidence-based studies makes it very challenging to continue building systems manually. The flexibility and moderate time for health experts to develop a CDSS is certainly one of the main reasons why rule-based systems are so widely used in smaller studies (usually IF–THEN rules), this is further supported by the fact that from the 341 possible relevant papers that were fully reviewed 114 were relevant and composed of primarily small studies, but when looking at rigorous evaluation, only 15 of those papers were in fact shortlisted and included in this study.

There were a number of interesting findings from this study. From the 15 papers shortlisted, there were no RCT or quasi-experimental studies and many of the papers only contained small-scale evaluations. No papers examined the costs of system implementation or carried out any form of cost/benefit analysis. Despite the fact that ontologies provide many advantages for representing domain knowledge, only 6 of the shortlisted papers used ontologies to represent domain knowledge. Given the obvious advantages to integrating the CDSS with the EHR system, only 2 of the papers described CDSSs that integrated with an EHR system and in general interoperability was not addressed. Technology standards are very important in the development of systems and can lead to faster development times, enhanced reliability, enhanced security and can result in safer software, however, only 3 of the shortlisted papers used recognised healthcare technology standards (and all these were HL7 standards).

Finally, as mHealth is changing the way healthcare is delivered, driven by increased mobile device penetration and capabilities along with growing clinician and patient demand, and an mHealth-based CDSS offers the potential to reduce medical errors and improve the quality and efficiency of healthcare, only 5 of the shortlisted papers supported mobile use. This point has also been noted by other researchers; for example, [49]. Moreover, given that the cloud does not only provide on-demand services but also offers high availability, reliability, vast scalability, a cheaper environment for computing, and we are seeing a move in healthcare to transform and shift IT structure towards the cloud, we might have expected to see more CDSSs using the cloud, however, out of the 15 selected papers only 1 paper used the cloud.

There were several relatively new non-knowledge based approaches briefly discussed in this paper that may address some of the complexities involved in decision making in healthcare. The automation of rule generation from analyzing a vast volume of evidence-based research and the correlation to each patients' health history can provide a more enriched diagnostic/prognostic tool for the future. With the increase in evidence-based clinical trials and in some cases the automatic translation to clinical knowledge it is possible that scalable nonknowledge based approaches may be better suited to tackle the increased complexity.

Recommendations arising from these findings suggest the following (see Fig. 3):

- At the outset of the development of the CDSS, a methodology has to be produced for how the system will be evaluated to demonstrate that the CDSS is effective and provides clear clinical benefits and cost benefits.
- Interoperability has to be addressed from the start of the development to ensure that the CDSS integrates with the EHR as well as other healthcare information systems.
- The adoption of relevant healthcare technology standards should underpin the development of the CDSS to enhance reliability, enhance security and provide safer software among other benefits.
- Ontologies facilitate standardization, flexibility for change, and promote sharing and reusability of medical knowledge between CDSS systems and their use should be considered in the development of a CDSS. The adoption of relevant publicly available ontologies should be considered first before any new ontologies are created.
- Consideration should be given to mobile usage given increased mobile device penetration and capabilities along with growing clinician and patient demand.
- Consideration should be given to whether the cloud provides any suitable services for the CDSS.
- As well as the use of traditional knowledge-based approaches to CDSS development, consideration should be given to the use of non knowledge based approaches where this may be more appropriate.

While these recommendations are not novel the findings from this review suggest these recommendations are not being addressed in the development of CDSSs. It is difficult to gauge from the papers why this might be the case but possible reasons may be the additional costs of addressing interoperability or using recognised CDSS standards; initial developments may only be prototypes to prove the underlying concept with a more extensive implementation to follow if the business case can be made; experimental studies can be difficult to undertake and require careful planning and approval from a range of different parties and may be considered beyond the scope of the project; projects may not have the appropriate staff for development or evaluation (eg [52, 53].).

In terms of limitations of the study, the review is based on a limited number of electronic databases and the inclusion of additional databases may identify further relevant papers.

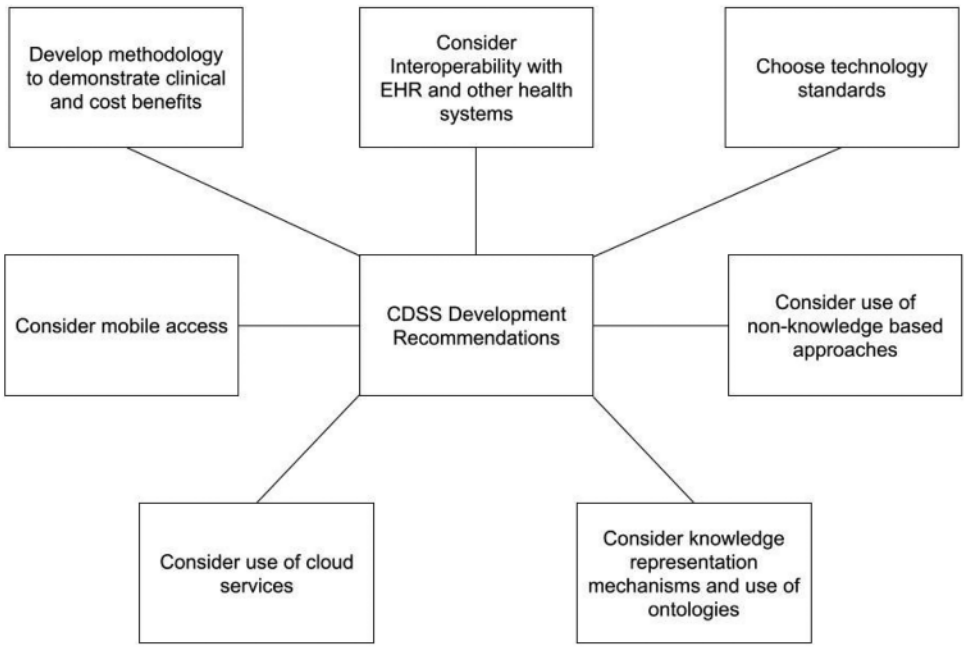

Fig. 3 Rule Based CDSS Recommendations

In addition, the majority of the work reviewed consisted of projects that were academic oriented, open sourced, vendor agnostic. This implies that commercial systems that are closed sourced have not been captured in this study. This may provide some explanation as one of the factors to the limited use of standards found and interoperability in this study.

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