Review

Using clinical reasoning ontologies to make smarter clinical decision support systems: a systematic review and data synthesis

Pavithra I. Dissanayake, Tiago K. Colicchio, and James J. Cimino

Informatics Institute, University of Alabama at Birmingham, Birmingham, Alabama, USA

Corresponding Author: Pavithra I. Dissanayake, DO, Informatics Institute, University of Alabama at Birmingham, 1900 University Boulevard, Suite 142, Birmingham, AL 35294-3412, USA; pidissanayake@uabmc.edu

Received 11 April 2019; Revised 20 July 2019; Editorial Decision 18 August 2019; Accepted 5 September 2019

ABSTRACT

Objective: The study sought to describe the literature describing clinical reasoning ontology (CRO)–based clinical decision support systems (CDSSs) and identify and classify the medical knowledge and reasoning concepts and their properties within these ontologies to guide future research.

Methods: MEDLINE, Scopus, and Google Scholar were searched through January 30, 2019, for studies describing CRO-based CDSSs. Articles that explored the development or application of CROs or terminology were selected. Eligible articles were assessed for quality features of both CDSSs and CROs to determine the current practices. We then compiled concepts and properties used within the articles.

Results: We included 38 CRO-based CDSSs for the analysis. Diversity of the purpose and scope of their ontologies was seen, with a variety of knowledge sources were used for ontology development. We found 126 unique medical knowledge concepts, 38 unique reasoning concepts, and 240 unique properties (137 relationships and 103 attributes). Although there is a great diversity among the terms used across CROs, there is a significant overlap based on their descriptions. Only 5 studies described high quality assessment.

Conclusion: We identified current practices used in CRO development and provided lists of medical knowledge concepts, reasoning concepts, and properties (relationships and attributes) used by CRO-based CDSSs. CRO developers reason that the inclusion of concepts used by clinicians’ during medical decision making has the potential to improve CDSS performance. However, at present, few CROs have been used for CDSSs, and high-quality studies describing CROs are sparse. Further research is required in developing high-quality CDSSs based on CROs.

Key words: clinical reasoning ontology, clinical decision support, clinical ontology, clinical concepts, ontology properties

INTRODUCTION

Clinical decision support systems (CDSSs), when integrated with electronic health record (EHR) systems, are an integral part of health information technology.1,2 CDSSs assist clinicians during the health-related decision-making process by presenting situation-specific clinical knowledge and patient information, in an appropriate format, at the appropriate time of the care process.2 Barriers to CDS development include lack of incentives, lack of standardized clinical terminology, outdated legacy EHR, lack of transferability of clinical decision support (CDS) logic from one system to another, lack of experts needed to translate medical knowledge into a CDS knowledge base (KB), and the low computer literacy of the end user.3

Clinicians encounter a significant number of alerts every day, and the usefulness of these alerts is questionable. Van der Sijs et al4 conducted a systematic review to assess physician response to drug
safety alerts and found that 49%-96% of alerts were overridden. Studies have noted that clinicians often override alerts that are considered clinically irrelevant, reveal information that is already known by the clinician, or do not take into account other relevant information pertinent to the case. An unfortunate unintended consequence of CDSSs is “alert fatigue,” due to their high false positive rate. Traditionally, alerts have been designed to follow a rigid decision tree accessing only specific and limited patient information. Hence, alert logic often misses important relevant patient information, leading to inappropriate alerting. Other factors contributing to high false positive rates include low alerting threshold, lack of personalization, lack of clinical importance, and inaccuracy per updated guidelines.

Alert-based CDSSs usually are comprised of 3 components: a KB (encompassing scientific and medical information, patient information from the EHR and CDS logic), a user interface that allows the user to communicate with the system, and an inference engine that allows the system to reason from the EHR and CDS logic, a user interface that allows the user to communicate with the system, and an inference engine that provides the platform for the functionality of the CDSS. Currently, much of the patient data within EHRs, especially reasons for clinicians’ decisions, are in unstructured text format. Most logic-based CDSSs that rely on structured data are unable to utilize data related to clinical reasoning because the clinical data present within the EHR and the data structure of the KB are insufficient for the effective function of traditional alert-based CDSSs.

One approach that developers have employed to improve CDSSs is to model clinical reasoning through ontologies to simulate the decision-making processes carried out by clinicians. Clinical reasoning is the process used by clinicians to obtain and analyze data to reach a decision regarding a patient. It requires general understanding of evidence-based medical knowledge and the ability to isolate relevant medical information related to the specific case, based on a specific patient’s information. In treating patients, clinicians are faced with questions such as “What is the patient’s diagnosis?” and “When did symptoms start?” They are also faced with more complex questions related to reasoning such as “Why was a particular medication given over another?” or “What were the other diagnoses considered?” The data structures currently used within EHRs do not lend themselves readily to identifying answers to questions regarding clinical reasoning. This limitation also cripples the KBs used by current CDSSs. An ontology that details clinical reasoning will allow us to categorize and organize these reasons, thereby making them available for CDSS, and forms the basis for a more sophisticated system that utilizes previous patient-specific clinician reasoning when alerting.

An ontology is a formal representation of knowledge within a domain; typically, a hierarchically arranged set of unique terms known as concepts, their attributes, and the semantic relationships between those concepts. Ontologies organize domain knowledge into structures that computers can read, and humans can understand. Clinical reasoning ontologies (CROs) represent the concepts used by clinicians reasoning about diagnostic and therapeutic interventions and making diagnoses. Patient-specific clinical data are mapped into these CROs to make them usable in clinical reasoning axioms and to allow for the description of clinical decisions. CROs capture clinicians’ reasoning process by defining clinical concepts, mapping patient data to these concepts, and the defining the semantic relationships between them. This data structure will enable the creation of a more personalized KB for CDSSs. For example, clinicians can indicate, when prescribing, that a certain medication should be prescribed to the patient even though the patient is on a medication that could potentially interact with the prescribed drug, because the patient has previously tolerated the medication combination. A CDSS could be designed to access this information and learn that although generally there is a drug-drug interaction, it is irrelevant for this patient, and therefore, do not alert. Thus, in utilizing CRO-based CDSSs, one could decrease the pernicious phenomena of overalerting, and mitigate alert fatigue by creating more personalized and smarter CDSSs.

The ability to reuse existing ontologies would reduce some of the barriers to the development of CDSSs and could possibly speed the development process. The Open Biological and Biomedical Ontology (OBO) Foundry, a collective that provides access to biological, biomedical, and clinical related ontologies, could be a potential source for a CRO. However, the ontologies in OBO tend to focus on a specific aspect of clinical entities rather than cognitive processes. For example, the Human Disease Ontology classifies human-related diseases according to their etiology and provides a standardized ontology of disease and phenotype terms that allow for semantic mapping of diseases across existing vocabularies.

Given the clinical importance of CRO-based CDSSs and lack of a comprehensive literature review of current research on CROs in CDSSs, we believe that a systematic review is needed that provides an overview of the existing CRO-based CDSSs, with a compilation and classification of the concepts and properties present within these ontologies. This paper represents such a review to identify and summarize published works that describe CDSSs based on clinical ontologies with a focus on ontologies that contain clinical reasoning concepts and semantic relationships. We included a catalogue of the concepts and properties used within these ontologies and identify the current practices for developing and applying CROs to CDSSs. The results of our study provide a resource for researchers and developers working on CRO-based CDSSs to select characteristics applicable to their efforts and can be used as a reference to guide future research and potential synergies of current practices in CRO-based CDSSs.

**MATERIALS AND METHODS**

We reviewed the literature with the objective of answering the following study questions:

1. What are the existing CROs used to empower CDSSs?
2. How are the CROs and the CDSSs evaluated by their developers?
3. What are the characteristics of the existing CROs that are used by researchers and developers working on CRO-based CDSSs (ie, medical knowledge concepts, reasoning concepts, semantic relationships, and attributes)?

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines as far as appropriate for this review, to minimize the selection bias of included studies.28 A study protocol was written before the investigation (the study protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and published systematic reviews before investigation and was submitted to PROSPERO to be registered; the study was deemed as outside PROSPERO’s scope).

Data sources and search strategy
We searched databases including PubMed, PubMed Central, and Scopus from their inception to January 30, 2019. Multiple search terms and combinations of search terms were tested to determine the search strategy that identified the broadest results possible. Consensus among the authors was reached before deciding on the search strings. MeSH (Medical Subject Headings) terms were not used in the search strings as they were found to identify many irrelevant studies. We found that including both singular and plural forms within the second query broadened the search and identified studies that would have otherwise been missed. We used the following search strings:

- PubMed and PubMed Central search terms:
  “Clinical cognition” OR “Clinical Reasoning” OR (“Ontology” AND “Evidence Based Medicine”)
- Scopus and Google Scholar (GS) search terms:
  (“Decision support system” OR “Decision support systems”) AND (ontology OR terminology)

We included GS as an additional source to capture any relevant “grey” literature. Grey literature comprises nonformal scholarly publications produced by organizations outside of traditional academic publishers and can include dissertations, technical reports, conference proceedings articles from nongovernmental organizations and policy institutions.29 Many innovations in technology are initially published in these forms. There are some limitations to GS (eg, the search algorithm can personalize the search to the user, thus hindering replicability).30 Additionally, studies on GS have suggested the search should be limited to the first few pages due to diminishing returns.31 Indeed, we found that the relevancy of the articles greatly diminished after 10 pages; hence, we confined our search results to first 10 pages. The final search was conducted on February 2, 2019.

Study selection
The identified studies were evaluated according to the inclusion criteria: (1) studies exploring terminologies related to clinical reasoning and CDS, (2) studies exploring application or development of CDSSs that use CROs or clinical ontologies with reasoning axioms, and (3) studies exploring computerized methodology to draw relationships between clinical concepts.

The study selection was performed in stages. In stage 1, eligibility criteria were refined by 2 authors (P.I.D., J.J.C.) who independently reviewed subsets of 100 titles. The percent agreement was calculated following the independent review. Disagreements were discussed with the aim of revising and fine-tuning the eligibility criteria. This process was repeated with the revised criteria and another subset of 100 titles until a 94% agreement was reached. In stage 2, the titles were assessed for inclusion by a single reviewer (P.I.D.). The abstracts of all selected articles during stage 2 were then evaluated in stage 3 independently by the 2 reviewers (P.I.D., J.J.C.). Articles accepted, based on abstracts, by either reviewer advanced to the fourth stage of screening, in which 2 authors (P.I.D., J.J.C.) screened the full text of each article. The final article list is a compilation of articles accepted by both reviewers during stage 4.

Data extraction and synthesis
Data related to CDSS purpose, medical domain, computational methods, ontology scope and purpose, knowledge source, and characteristics such as concepts (medical knowledge and reasoning) and properties (relationship and attributes) were extracted from the study articles. The information provided within the articles was abstracted using an iteratively structured form by one of the authors (P.I.D.). The ontologies were categorized as new, existing, or revised based on whether the study article described using an ontology newly created by the CDS development team, used an existing ontology without modification, or used an existing ontology but modified to better fit CDSS scope, respectively. The other authors were consulted, as needed, for data extraction, and any conflicts were resolved via discussion and consensus.

We compiled concepts and properties used within the CRO. We reached group consensus about the classification of properties as either “relationships” or “attributes” and concepts as either “reasoning concepts” or “medical knowledge concepts.” We combined the concepts and removed duplicates based on the descriptions provided within the text, tables, and concept maps provided in the publications. When necessary, a more descriptive term was used to identify the final concept based on its description. The same methodology was performed for properties. When a definition of a concept or property was unavailable within the article, we inferred the definition using the informed assessment of the 2 medical expert authors.

Last, we extracted data regarding the CDSSs, and any ontology evaluations performed by the development team (internal validity and usability testing). See Supplementary List 1 for definitions of characteristic terms.

Quality assessment
The ontology evaluation comprises intrinsic (ie, technical) and extrinsic (ie, usability) testing. We defined intrinsic evaluation as an assessment of the ontology based on a set of criteria: accuracy, clarity, internal consistency, completeness, conciseness, expandability, and efficiency.32,33 Extrinsic evaluation relates to function and is defined as measurement of effectiveness of the CRO-based CDSS and its ease of use.34 We based our definitions of evaluation criteria established by Gomez-Perez.32

We conducted the quality assessment by evaluating the quality related data described in the publications. Any mention of performance of accuracy, clarity, internal consistency, completeness, conciseness, expandability, or efficiency were grouped under intrinsic evaluation as per our definition, and any mention of use testing were categorized as extrinsic. We conducted our evaluation based on predefined criteria as indicated in Figure 1. The CDSSs were then categorized as high, moderate, or low level of quality. Owing to the descriptive nature of the included studies, the Cochrane risk of bias is not applicable.

RESULTS
The database searches yielded a total of 7770 results. After excluding duplicates and articles in which the full-text version was not
available in English, we reviewed 7119 titles. Of these, 470 articles met eligibility criteria for abstract review, which led to 179 articles for full-text review. Forty studies met the inclusion criteria and were reviewed in detail. The selection of articles is outlined in Figure 2.

Characteristics of CDSSs
The characteristics of the CRO-based CDSSs are summarized in Table 1. The articles by Farrish and Grando and by Grando et al. described the same CRO-based CDSS; hence, they were combined, resulting in 38 CRO-based CDSSs. All of the final 40 articles were found in either MEDLINE or Scopus. None of the final articles were exclusive to GS.

Rule-based computational methods use IF/THEN logic rules for inferencing. Ontology-based methods make inferences by following the relationships within the ontology. In addition, “algorithm” was used to describe when an inference was based on a specific calculation. Thirty CDSSs (79%) used rule-based computation for inferencing, 22 (58%) used an ontology-based method, 6 (16%) used algorithms, 3 (8%) used natural language processing, 3 (8%) used

---

Table 1: Characteristics of CRO-based CDSSs

| Total Grade | Level of quality |
|-------------|-----------------|
| A or B or AC or BC and C 10 or 0 1 | Strong |
| A 11 or B 11 or AC 11 or BC 11 | Medium |
| C 10 or C 0 1 | Weak |
| D 0 0 | None |

---

Figure 1. Criteria used for study quality assessment.

Figure 2. Search results.
| Author                  | Computational methods | Medical domain     | CDSS purpose                                                                 | Associated ontologies                                      |
|------------------------|-----------------------|--------------------|-------------------------------------------------------------------------------|------------------------------------------------------------|
| Mohammed and Benlamri  | RB, proximity-based, machine learning | DM2 and HTN        | Provides differential diagnosis recommendation based on patient’s data and CPGs | Patient ontology, disease symptoms ontology                |
| Sene et al             | RB, pattern-matching algorithm, NLP | Geriatric oncology | Assist during telemedicine based on CBR process and the conventional medical reasoning | Medical ontology                                           |
| Denekamp and Peleg      | Multiphase, anchor-based, Bayesian | Diagnosis          | Assist physicians in the process of MCM-oriented diagnosis                    | TiMeDDx - Knowledge model                                  |
| Uciti et al             | RB                     | Perioperative risk  | Identify and analyze risks in perioperative treatment process to aid in avoiding errors | Risk identification ontology (RIO)                         |
| Bau et al              | RB                     | Diabetic management during surgery | Assist with the management of diabetic patients during surgery | Domain ontology                                           |
| Merlo et al             | OB                     | Functional behavioral problems | Provide an evidence-based approach to behavioral experts in diagnosing behavioral problems | FBA ontology                                               |
| Jimenez-Molina et al    | OB, fuzzy logic, algorithm | Chronic disease    | Manage all stages of chronic patient diagnosis and treatment based on business process management approach | MCCS ontology, process ontology, actors ontology          |
| Shen et al             | OB, machine learning   | Infectious diseases | Diagnose infectious diseases based on patient entered data and provide antibiotic treatment recommendations | Domain ontology                                           |
| El-Sappagh et al       | OB, RB                 | DM2                | Assists with the treatment of DM2                                             | DM2 Treatment Ontology (DMTO)                              |
| Abidi                  | OB, RB, algorithm      | Comorbidity conditions | A CPG integration framework to provide primary care physicians, institutional specific CPG medicated CDSs for comorbidities | Comorbidity CPG ontology                                   |
| Beierle et al          | OB                     | BC                 | Support treatment decisions in cancer therapy by revising co-medications and drug interactions | Ontology for Cancer Therapy Application                   |
| Shang et al            | RB                     | Chronic disease (HTN and DM2) | Service oriented sharable CDSS that integrates multiple CPGs, for chronic diseases | Infrastructure ontology, special ontology                  |
| Berges                 | OB                     | GHJ rehabilitation | Assist physiotherapists during the treatment processes related to GHJ          | Telerehabilitation Ontology (TrhOnt)                      |
| Qi et al               | RB                     | SpA                | Provides patients with a personalized home-based self-management system for SpA | SpA ontology                                               |
| Alsomali et al         | RB                     | Penicillin-related adverse events | Alert clinicians of possible adverse drug events related to penicillin during drug prescription | Ontology of penicillin allergy                             |
| Zhang et al            | RB                     | CPG                | A sharable CDSS for management of clinical pathways that integrates into hospital CDS applications and fits into existing workflows | Decision support knowledge base generic ontology          |
| Wilk et al             | OB, RB                 | IHTs               | Assist with formation of the IHTs to manage patients based on presentation-specific clinical workflows and team dynamics | IHT ontology                                               |

(continued)
| Author               | Computational methods | Medical domain | CDSS purpose                                                                 | Associated ontologies                                      |
|----------------------|-----------------------|----------------|--------------------------------------------------------------------------------|----------------------------------------------------------------|
| Zhang et al48        | RB, OB                | DM2            | Provides patient specific recommendations on the management of inpatients with DM2 | Semantic healthcare knowledge ontology                     |
| Rosier et al49       | RB, OB                | Cardiology     | Improve AF-related CIED alert triage                                           | Cardio-vascular disease ontology                           |
| Jafarpour et al50    | RB, OB, algorithm      | CPG            | Provide computerized CDS based on CPGs using an OWL-based execution engine     | CPG ontology                                               |
| Alharbi et al51      | RB                    | Diabetes       | Decision support for diagnosis and treatment of diabetes based on CPG          | Diabetes Ontology, Patient ontology                        |
| Shen et al14         | OB, machine learning, NLP, fuzzy logic | Disease diagnosis and treatment | Provides clinicians and patients with an optimal personalized diagnostic and treatment plan | Knowledge Model Agent Type (KMAT) ontology |
| El-Sappagh et al52   | RB                    | Diabetes       | Assist with the diagnosis and management of diabetes                           | Case base ontology                                         |
| Budovec et al26      | RB                    | Radiology      | Provides radiology differential diagnosis in an interactive website and an educational tool | Radiology Gamuts Ontology (RGO)                            |
| Wang et al53         | RB, probability       | General medical CPGs | Personalized CPGs for disease specific treatment to be used by individual hospitals. | Local ontology                                             |
| Eccher et al54       | RB, OB                | Cancer therapy | Facilitate the interoperability between a CPG-based DSS for cancer treatment and an oncological EPR | Therapies ontology                                         |
| Martínez-Romero et al55 | RB, OB              | CICU           | Provides supervision and treatment assistance for critical patients in CICU with acute cardiac disorders | Critical Cardiac Care Ontology (C3O)                        |
| Farrish and Grando56, Grando et al57 | RB              | Medication     | Assists with management of polypharmacy prescriptions for patients with MCC to reduce the overall treatment complexity | Drug ontology                                              |
| Omaish et al58       | RB, OB                | ACS            | Assists ED physicians with treatment of ACS patients based on computerized ACS CPGs | CPG ontology                                               |
| Riaño et al59        | OB, ranking of weighted options | Home care of chronic diseases | Assists with the management of chronically ill patients including development of personalized treatment plans | Case profile ontology                                     |
| Adnan et al (2010)60 | OB, NLP, RB           | High risk discharge medications | Provides advice recommendations for high risk discharge medications, to be used in the Electronic Discharge Summary | Medication information ontology                             |
| Precila et al61      | RB                    | Heart failure CPGs in Imaging studies | Provides CDS for heart failure CPGs in Imaging studies | Heart failure ontology                                      |
| Hussain and Abidi62  | RB                    | CPG            | Provides a framework to computerize CPGs and to execute modeled CPGs based on patient data to deliver recommendations | CPG ontology, domain ontology, patient ontology            |
| Abidi63, Abidi et al64 | RB              | BC             | An interactive BC follow-up CDSS for family physicians to assist with BC       | CPG ontology, patient ontology, BC ontology                |

(continued)
Characteristics of CROs

All the CROs were used as the KB for their respective CDSS. A total of 34 CDSSs (90%) used only 1 ontology, 4 CDSSs used 2 ontologies, and 2 CDSSs used 3 ontologies (Table 2). The ontology scope correlated with the medical domain. The types of knowledge sources employed during the ontology development (with the corresponding number of ontologies) included domain experts (n = 23), clinical pathway guidelines (CPGs) (n = 22), literature (n = 20), existing ontologies or terminologies (n = 14), EHR (n = 11), clinical workflows (n = 2), and software including websites (n = 1). Most CDSSs (81%) employed multiple sources with only 7 studies using 1 type of knowledge sources (4 using CPG only, 2 using existing ontology, 1 using literature). The size of the ontologies appears to vary significantly, although most publications did not mention the actual number of concepts and properties.

Quality assessment data

Our quality assessment revealed that 30 (79%) studies described the evaluation of the CRO-based CDSS. In 29 (76%) cases, intrinsic evaluations were performed and 20 (53%) studies employed test cases or comparison studies. A test case was defined as a set of variables under which the system’s function is tested. For example, the accuracy of TiMeDDx was tested by analyzing the diagnosis inferred for patient vignettes describing multiple symptoms. Comparison studies compared the outcome of the CDSS with a gold standard, domain expert, or another CDSS. For example, in the article by Shen et al., the system’s diagnostic capability was tested by comparing the diagnosis of the CDS to that of the clinician.

Nine of the publications mentioned performing intrinsic evaluation but did not elaborate the purpose. Usability testing was only performed in 6 CDSSs. Only 5 studies achieved a high quality level, while 10 had a medium quality level, and 23 had a weak quality level. Our assessment revealed that 8 studies did not report a formal evaluation of their CDS or CRO. The CRO-based CDSSs in our study set did not discuss testing related to clinical salience in practice or effects on clinical outcomes. Figure 3 summarizes the quality assessment of included studies.

Concepts and properties extracted from CROs

A total of 1315 concepts and 603 properties were identified from the study articles. We then removed duplicates and combined concepts with similar descriptions, producing a final list of 567 concepts. These were then categorized into 339 medical knowledge concepts. We considered concepts that describe medical knowledge concepts and 31 subconcepts. For example, we considered concepts such as patient history and history under the concept history; concepts route of administration, delivery option, and application route under the concept route of administration; and concepts rule, logic, and SWRL: Rule under the concept Logic. We determined that the concepts comprised 15 medical domains. See Supplementary Table S1 for full list of the medical knowledge concepts.
| Author                        | Ontology scope                                                                 | Sources of knowledge | Ontology—source(s)a | Ontology sizeb Concepts | Properties |
|------------------------------|--------------------------------------------------------------------------------|----------------------|---------------------|-------------------------|------------|
| Mohammed and Benlamri11      | Patient parameter; diseases and symptoms                                      | Existing ontologies  | Multiple existing plus new | 241b         | 13 **       |
| Sene et al12                 | Medical concepts in geriatric oncology                                         | Lit, domain experts | New                 | 61b          | ND         |
| Denekamp and Peleg11         | Clinical data items related to diagnosis                                       | Lit, CPG, domain experts | New                 | 5b           | 6 **       |
| Ucic et al12                 | Perioperative risk                                                             | CPG, domain experts, existing ontology | Multiple existing | 19b         | 13b        |
| Bau et al16                  | Medical knowledge related to DM2 management                                    | Domain expert, EHR, hospital clinical workflow | New                 | 31b         | 13b        |
| Merlo et al17                | Structure and the semantics of functional behavioral assessment methods       | Domain experts, lit | New                 | 15b         | 15b        |
| Jimenez-Molina et al18       | Medical context; clinical pathways; healthcare professionals                  | CPG, domain experts, EHR | New                 | 24b         | 24b        |
| Shen et al19                 | Infectious disease                                                             | Existing ontologies, lit, CPG, websites | New                 | 1,267,004    | 12b        |
| El-Sappagh et al40           | DM2                                                                             | Lit, CPG, domain experts, EHR, existing ontologies | Multiple existing | >10,700      | 279        |
| Abidi31                      | CPG                                                                            | CPG, domain experts | New                 | 102         | 58         |
| Beierle et al42              | Cancer drugs: active ingredients, interactions, drug regimens                  | Lit, EHR, existing software | Revised existing | 40b         | 18b        |
| Shang et al43                | HTN and DM2 disease concepts related to HTN and DM2                           | CPG                  | New                 | 47          | 121        |
| Berges44                     | Physiotherapy process related to glenohumeral joint                            | Existing ontologies and databases, EHR treatment protocol, domain experts | Multiple existing | 2,351       | 100        |
| Qi et al45                   | Spondylarthrits and definitions for alert type                                 | Lit, CPG, domain experts | New                 | 22b         | 22b        |
| Alsomali et al46             | Penicillin allergy related adverse events                                       | Lit, existing ontologies | New                 | 52          | 15         |
| Zhang et al47                | Patient data, CDS related domain knowledge, CDS rules                          | CPG                  | New                 | 62          | 94b        |
| Wilk et al27                 | Clinical workflow, interdisciplinary healthcare team member and patient specific concepts | Lit, domain experts | Revised existing | 21b         | 19b        |
| Zhang et al48                | DM2                                                                             | Lit, CPG, EHR, domain experts, existing terminologies | New                 | 127         | 196        |
| Rosier et al49               | AF and CIED alerts                                                             | Lit                  | New                 | 252         | 25         |
| Jafarpour et al50            | Nursing, CHF, and AF CPGs                                                      | Existing ontology   | Revised existing    | 12b         | 13b        |
| Alharbi et al51              | Diabetes                                                                        | CPG, domain experts | New                 | 7b          | 19         |
| Shen et al14                 | Diagnosis, prognosis, and treatment (example: gastric cancer)                  | Lit, EHR            | New                 | 92b         | 58b        |
| El-Sappagh et al52           | Case base reasoning context in diabetes; patient attributes                    | Domain experts, lit, CPG, existing ontology, EHR | Multiple existing | 132         | 48b        |
| Budovec et al26              | Radiology information needed for diagnosis                                      | Lit, domain experts | New                 | 4b          | 3b         |
| Wang et al53                 | CPG                                                                             | EHR, CPG, domain experts | New                 | 88b         | 11b        |
| Eccher et al54               | Cancer treatment                                                                | Domain experts, oncological workflows, existing ontologies | New                 | 82b         | 9b         |

(continued)
Reasoning concepts were also categorized by removing duplicates and combining the concepts with the same definition. For example, we grouped concepts *ActDocumentation* and *Make record of data* under the concept *Data documentation*; concepts *task* and *enact tasks* under the concept *enact tasks*; and concepts *Application_purpose*, *Therapeutic purpose*, and *Treatment_intent* under the concept *Treatment_purpose*. Thirty-eight unique reasoning concepts with 86 subconcepts were identified. The reasoning concepts expanded over 5 medical domains. See Table 3 for full list of reasoning concepts and Supplementary Table S2 for their definitions.

Properties were also analyzed in similar fashion leading to 240 unique properties: 103 attributes and 137 relationships. The properties comprised relationships and attributes across 17 domains. Table 4 displays a sample list of properties, their facets, and their designation as attribute or property (see Supplementary Table S3 for the full list).

### DISCUSSION

In this systematic review, we investigated the literature exploring CROs used to empower CDSSs. We assessed the characteristics of the existing CDSSs that use CROs and determined the current practices used by the developers in creating the CROs. Tables 1 and 2 list the key findings. In summary, although there are many clinical ontologies in existence, we only identified 38 studies that used them in CDSSs. Moreover, these CROs restricted themselves to a specific clinical workflow. Ontologies such as the Breast Cancer Ontology (BCO) and DMTO only contain concepts related to a specific disease, whereas ontologies like RIO and C3O are restricted to specific workflows within a specific subspecialty. These limitations are understandable considering the enormity of the medical field. The restricted scope of the ontologies limits their applicability across the full medical domain.

Medical decisions involve complex inferential processes, some, if not all, at least in part use “reasoning.” The difficulty in developing...
a sophisticated CDSs that only alerts the clinician when appropriate, reducing the need for overrides, or assists with complex decision-making processes such as providing a differential diagnosis that is personalized to each patient, lies with the difficulties associated with decoding what constitutes clinical reasoning. Many researchers have proposed different approaches for utilizing ontologies to decrypt clinical reasoning especially for the betterment of CDSs. We noted that even when CDSs use CROs, most of them do so in combination with other inferencing methods such as rule-based inferencing to adequately represent the knowledge needed for the CDS. This finding is expected given the complexity associated with clinical reasoning and KBs.
Our analysis also revealed that most developers referred to multiple data sources during ontology development, including existing ontologies, domain experts, literature, clinical guidelines, and the EHR. Currently, however, there is neither a standard format to identify appropriate sources for an ontology nor a standard document to which developers can refer to as a starting point. CROs and CRO-based CDSSs are generally being developed and studied in isolation. We believe that the broader informatics community will benefit from knowing the best practices used by existing systems. More importantly, our study provides a list of concepts and properties for an initial starting point, as is found in other research fields such as drug development or genetic research. We note, for example, that there are multiple ontologies developed by different groups for clinical workflows related to breast cancer\(^{25,42,63-65}\) and diabetes.\(^{11,36,40,48,52}\) As such, we believe that our lists of medical knowledge concepts, clinical reasoning concepts, and properties will provide a foundation for starting the development process of future ontologies. Furthermore, our findings could be used as the basis for a standard to improve access to data by CDSS developers, implementers, or evaluators to improve the function and interoperability of EHR and CDSS.

### Implications for EHR improvement and future research

Clinical ontologies are increasingly used as a means for improving various aspects of health care.\(^{66-70}\) CDS is one such area in medicine in which clinical ontologies are being used to develop more efficient and accurate systems. Most CROs focused on a specific disease process, workflow, or subspecialty; hence, they tend to only map clinical reasoning concepts and relationships related those aspects. Thus, most CROs create only a partial representation of clinical knowledge used by clinicians. A more comprehensive CRO will facilitate better structuring of the KB and allow CDSSs to access a wider range of information that can both complement and improve extant systems.

### Figure 3. Quality assessment of the clinical decision support systems and their ontologies.

| Evaluators                                                                 | Intrinsic evaluation | Usability testing | Total grade | Quality level |
|----------------------------------------------------------------------------|----------------------|-------------------|-------------|---------------|
| Mohammed & Benlamri (2014)                                                 | A                    | 1                 |             |               |
| Sene et al (2015)                                                          | C                    | 1                 |             |               |
| Denekamp & Polge (2010)                                                    | C                    | 1                 |             |               |
| Ucetl et al (2017)                                                         | AC                   | 1                 |             |               |
| Bau et al (2014)                                                           | A                    | 1                 |             |               |
| Merlo et al (2018)                                                         | AC                   | 1                 |             |               |
| Jimenez-Molina et al (2018)                                                | AC                   | 1                 |             |               |
| Shen et al (2018)                                                          | C                    | 1                 |             |               |
| El-Sappagh et al (2018)                                                    | C                    | 1                 |             |               |
| Abidi (2017)                                                               | AC                   | 1                 |             |               |
| Beierle et al (2017)                                                       | D                    | 0                 |             |               |
| Shang et al (2017)                                                         | C                    | 1                 |             |               |
| Berges (2016)                                                              | C                    | 1                 |             |               |
| Qi et al (2016)                                                            | C                    | 1                 |             |               |
| Alsonali et al (2016)                                                      | C                    | 1                 |             |               |
| Zhang, Gou, et al (2016)                                                   | AC                   | 1                 |             |               |
| Wilk et al (2016)                                                          | C                    | 1                 |             |               |
| Zhang, Tian, et al (2016)                                                  | AC                   | 1                 |             |               |
| Rosier et al (2016)                                                        | C                    | 1                 |             |               |
| Jafarpour et al (2016)                                                     | AC                   | 1                 |             |               |
| Alharsi et al (2015)                                                       | C                    | 1                 |             |               |
| Shen et al (2015)                                                          | AC                   | 1                 |             |               |
| El-Sappagh et al (2014)                                                    | AC                   | 1                 |             |               |
| Budovec et al (2014)                                                       | D                    | 0                 |             |               |
| Wang et al (2014)                                                          | D                    | 0                 |             |               |
| Eccher et al (2011)                                                        | C                    | 1                 |             |               |
| Martinez-Romero et al (2013)                                               | C                    | 1                 |             |               |
| Farrish & Grando (2013), Grando et al (2012)                               | C                    | 1                 |             |               |
| Ouaish et al (2012)                                                        | A                    | 1                 |             |               |
| Rialro et al (2012)                                                        | AC                   | 1                 |             |               |
| Adnan et al (2010)                                                         | D                    | 0                 |             |               |
| Preel et al (2008)                                                         | D                    | 0                 |             |               |
| Hussain & Abidi, 2008                                                      | A                    | 1                 |             |               |
| Abidi, 2007; Abidi et al, 2007                                              | D                    | 0                 |             |               |
| Fox, 2004                                                                  | D                    | 0                 |             |               |
| Achour et al, 2001                                                         | C                    | 1                 |             |               |
| Wheeler et al, 2018                                                       | B                    | 0                 |             |               |
| Sadki et al, 2018                                                          | D                    | 0                 |             |               |
| Domain                | Property                              | Facet                          | Range       | R vs. A |
|----------------------|---------------------------------------|-------------------------------|-------------|---------|
| Record               | has_Patient                           |                               | Medical record | A       |
|                      | hasHighLevelContext                   |                               | High-level context | R       |
| Patient              | has_patient_profile                   |                               | Patient properties | R       |
|                      | has_patient_ID                        |                               | Patient ID | A       |
|                      | has_lab_test                          | has_Part, has_Unit, has_Status | Lab test details | R       |
|                      | has_Lab_test_value                    |                               | Test value | A       |
|                      | has_diagnosis                         | hasSide                       | Diagnosis, location | R       |
|                      | has_diagnosis_severity                |                               | Disease severity | A       |
|                      | has_history                           | EndingDate                    | Patient’s history | R       |
|                      | has_Family_History                    | isRelativeOf                  | Family history | R       |
|                      | has_treatment_plan                    |                               | Treatment plan | R       |
|                      | has_symptom_or_sign                   |                               | Symptoms and sign | R       |
|                      | has_description                      |                               | Chief presentation | R       |
|                      | has_measurement                       | has_UpperLimitValue, has_ExactValue | Value | A       |
|                      | Disease_since_date                    |                               | Date | A       |
|                      | has_complication                      |                               | Complication | R       |
|                      | has_previous_treatment_plan           |                               | Treatment plan | R       |
|                      | has_HealthcareProvider                | hasSpecialty, plays_role_of, actorName | Healthcare provider | R       |
|                      | has_Assessment                        | hasName, Sex, has Age, Ethnicity | Demographic data | R       |
|                      | has_measurement                       | has_UpperLimitValue, has_ExactValue | Value | A       |
|                      | has_complication                      |                               | Complication | R       |
|                      | has_Disease_since_date                |                               | Date | A       |
| Diagnostic process   | observationMethod                     |                               | Observation method | R       |
|                      | observed_data                         |                               | Data value | A       |
|                      | Assessment_Reason                     |                               | Reason | R       |
|                      | has_pain                              |                               | Pain level | A       |
|                      | has_device                            | hasMedicalDevice, hasTool     | Medical device | R       |
|                      | has_Assessment                        |                               | Assessment | R       |
|                      | has_patient_reported_findings         | has_VAS_value, has_ASDAS, etc | Questionnaire value | A       |
|                      | has_Recommendation                    |                               | Recommendation | R       |
| Signs and symptoms   | is_assessed_by                        |                               | Assessment name | R       |
|                      | has_RecoveryRate                      |                               | Recovery rate | A       |
|                      | has_MortalityRate                     |                               | Mortality rate | A       |
|                      | is_not_caused_by                      |                               | Factors | R       |
|                      | cause_by                              |                               | Causing factor | R       |
|                      | is_symptom_of                         |                               | Disease | R       |
| Diagnosis and disease| hasSyndrome                           |                               | Syndrome name | R       |
|                      | has_severity                          |                               | Severity level | A       |
|                      | has_treatment                         | antibiotic2bacteria           | Treatment | R       |
|                      | has_causation_factors                | bacteria2infection            | Causing factor | R       |
|                      | hasRisk                               |                               | Risk factor | R       |
|                      | affected_Body_Site                    |                               | Body part | R       |
|                      | hasLabTest                            |                               | Lab test name | R       |
|                      | Status                                |                               | Status | A       |
|                      | hasSyndromeDuration                   |                               | Time | A       |
|                      | has_new_stage                         |                               | Cancer stage | A       |
|                      | is_transmitted_by                     |                               | Vector | R       |
|                      | has_complication                      |                               | Complication list | R       |
|                      | occurs_with                          |                               | Disease, symptom | R       |
|                      | hasExperimentalData                  |                               | Experimental data | R       |
| Treatment            | hasHealthRecord                       | hasEHR_ID                     | Health record ID | A       |
|                      | has_education_program                 | has_provider, has_section     | Education program | R       |
|                      | has_next_evaluation_date              |                               | Date | A       |
|                      | part_of                               | part_of                       | Treatment plan | R       |
|                      | has_intervention_goal                 | isAppropriateForInterventionGoal | Intervention goal | R       |
|                      | has_pharmacological_plan              |                               | Medication list | R       |
|                      | is_recommended_for_illness            |                               | Recommendation | R       |
| Medication           | Can_be_combined_with                  |                               | Medication | R       |
|                      | Contradict_with                       | Contradict_with_drug, _with_drug | Drug ingredient | R       |
|                      | has_treatment_target                  | has_A1C_lowering_level, etc   | Treatment target | A       |
|                      | has_active_ingredient                 |                               | Active ingredient | A       |
|                      | has_administrationProcess             |                               | Administration process | R       |
|                      | has_cost                              |                               | Medication cost | A       |
|                      | has_order_start_date                  |                               | Date | A       |
CDSSs without being restrictive to only one aspect of patient care.\textsuperscript{71} This inclusiveness would allow for the development of more complex CDSSs that can incorporate and act upon data related to the whole patient. In turn, CDSSs could be better personalized to provide alerts only when they are clinically relevant to the patient. This would lead to significantly fewer alerts and alleviate alert fatigue.

Developers of clinical ontologies and CDSSs should consider expanding the number and the types of reasoning concepts mapped in CROs. In our study, we identified 38 unique reasoning concepts that belonged to 5 medical domains. An expanded CRO can be used to identify and store reasoning behind many medical decisions that currently are only present in the free-text clinical notes (ie, history and physical examination, progress notes, consult notes, pathology.

Table 4. continued

| Domain               | Property                      | Facet                                      | Range          | R vs. A |
|----------------------|-------------------------------|--------------------------------------------|----------------|--------|
|                      | has_order_stop_date           | date                                       | A              |        |
|                      | has_dose                      | hasPatientDrugUnRec, etc                   | Dose           | A      |
|                      | dosage_Measurement_Unit      | measurement unit                           | A              |        |
|                      | has_cumulative_dose           | accumulative dose                          | A              |        |
|                      | has_maximum_dose             | maximumDrugUnits, maximumDosage           | R              |        |
|                      | has_frequency (freq)         | maximum_Freq, minimum_Freq                | Drug frequency | A      |
|                      | has_application_route        | Drug application route                     | A              |        |
|                      | has_explanation              | Explanation                                 | R              |        |
|                      | has_toxicity                 | Toxicity                                   | A              |        |
|                      | has_Therapy_description      | withSpecificFluids                         | Drug therapy direction | A |
|                      | Nutrition                    | has_amount                                 | Quantity       | A      |
|                      | has_calories                 | has_total_calories                         | A              |        |
|                      | Time                          | number_of_times, hasExerciseTime           | Time           | A      |
|                      | has_temporal_entity          | Temporal data                              | A              |        |
|                      | has_temporal_relation        | equals, before, after, hasBeginning        | R              |        |
|                      | Trend_in_TimePeriod          | Time period                                | A              |        |
|                      | Alert                         | has_Alert                                  | Alert level    | A      |
|                      | AssociatedToDynamicContext   |                                            | Dynamic context | R |
|                      | Anatomy                       | nerve_supply                               | nerve          | R      |
|                      | has_location                 | Anatomic location                          | R              |        |
|                      | CDS/CPG                       | has_input                                  | CDS input      | A      |
|                      | has_Outcome                  | Outcome specification                      | A              |        |
|                      | hasDecisionRule              | CDS function, logic                        | R              |        |
|                      | has_Trigger                  | CDS trigger                                | A              |        |
|                      | has_logic_component          | Arc, hasEndNode, hasStartNode              | A              |        |
|                      | hasInformationReturn         | Treatment information                      | R              |        |
|                      | Risk                          | risk_for_adverse_situation                | Risk situation | R |
|                      | Risk_related_recommendation   | Diagnostic test                            | R              |        |
|                      | Clinical Team                | executes                                   | Clinical workflow | R |
|                      | hasPractitionerStatus        | Practitioner status                        | R              |        |
|                      | has_Action                   | has_directive, hasPatientAction, etc       | Action         | R      |
|                      | Task                          | Evokeles                                   | Diagnosis      | R      |
|                      | Synergistically_evoke        | Diagnosis                                  | R              |        |
|                      | hasCondition                 | Medical condition                          | R              |        |
|                      | has_status                   | Task status                                | R              |        |
|                      | is_followed_by               | Decision option                            | R              |        |
|                      | has_decision_option          | Relationship type                          | R              |        |
|                      | has_act_relations            | Medical team member                        | R              |        |
|                      | is_assigned                  |                                          |                |        |
|                      | Universal                    | Priority level                             | A              |        |
|                      | Priority                     |                                          |                |        |
|                      | Reason                       | isWarrantedBy                              | Reason         | R      |
|                      | hasFunction                  |                                          | Function       | R      |
|                      | isInputOf                    |                                          | Indicator      | R      |
|                      | isOutputOf                   |                                          | Output         | R      |
|                      | Functional terms             |                                          |                |        |
|                      | description                  |                                          | Rule description, model | R |
|                      | attribute                    |                                          | Attribute of model | A |
|                      | hasDataCategory              | subclass, hasScenario                      | Subclass, scenario | R |
|                      | terminologyName              |                                          | Name string    | A      |
|                      | code                         | procedureCode, DisplayName                | Code           | A      |
|                      | hasStructuredData            |                                          | Data type      | A      |
|                      | translation                  |                                          | Translating code | A |

A: attribute; ASDAS: Ankylosing Spondylitis Disease Activity Score; CDS: clinical decision support; CPG: clinical pathway guideline; R: semantic relationship; VAS: visual analog scale.
CONCLUSION

This review summarizes existing literature on CRO-based CDSSs. It identifies the current practices used within the development of the CROs and formulates lists of medical knowledge concepts, reasoning concepts, and properties (relationships and attributes) used by these CDSSs. The use of CROs, which map concepts used by clinicians’ during medical decision making, can significantly improve CDSS functionality. Although many CDSSs have been developed using clinical ontologies, few use CROs. As a result, high-quality studies describing CROs are sparse. Further research is required in developing high quality CRO-based CDSSs.

FUNDING

The work was supported, in part, by funds from the UAB Informatics Institute, as well as by National Center for Advancing Translational Sciences, of the National Institutes of Health, award number UL1TR003096 (to JJC). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

AUTHOR CONTRIBUTIONS

PID and JJC conceptualized, designed, and conducted the study including study selection, data extraction, and data analysis. PID drafted the manuscript with significant intellectual input form JJC, and JJC and TKC assisted with creating and editing the article. All authors approved the final version of the article.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Journal of the American Medical Informatics Association online.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Osheroff JA, Teich JM, Levick DL, et al. Improving Outcomes with Clinical Decision Support: An Implementer’s Guide. 2nd ed. Chicago, IL: Healthcare Information and Management Systems Society; 2012.
2. Berner ES, La Lande TJ. Overview of clinical decision support systems. In: Berner ES, ed. Clinical Decision Support Systems Theory and Practice. 2nd ed. New York, NY: Springer; 2007: 3–18.
3. Middleton B, Sittig DF, Wright A. Clinical decision support: a 25 year retrospective and a 25 year vision. Yearb Med Inform 2016; Suppl 1: S103–16.
4. Van der Sips H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006; 13 (2): 138–47.
5. McCoy AB, Thomas EJ, Krousel-Wood M, et al. Clinical decision support alert appropriateness: a review and proposal for improvement. Ochsner J 2014; 14 (2): 195–202.
6. Taylor L, R T. Reasons for physician non-adherence to electronic drug alerts. MedInfo 2004: 1101–5. http://moxxi.mcgill.ca/sites/moxxi.mcgill.ca/files/PDF-MEDINFO.pdf. Accessed March 12, 2019.
7. Kesselheim AS, Cresswell K, Phansalkar S, et al. Clinical decision support systems could be modified to reduce ‘Alert Fatigue’ while still minimizing the risk of litigation. Health Aff 2011; 30 (12): 2310–7.
8. Dissanayake PI, Kochendörfer KM. Clinical decision support systems in medicine. In: Brown GD, Pasupathy KS, Patrick TB, eds. Health Informatics, a Systems Perspective. 2nd ed. Chicago, IL: Health Administration Press; 2018: 121–46.
9. Nanji KC, Slight SP, Seger DL, et al. Overrides of medication-related clinical decision support alerts in outpatients. J Am Med Inform Assoc 2014; 21 (3): 487–91.
10. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians’ decisions to override computerized drug alerts in primary care. Arch Intern Med 2003; 163 (21): 2625–31.
11. Mohammed O, Benlamri R. Developing a semantic web model for medical differential diagnosis recommendation. J Med Syst 2014; 38 (10): 79.
12. Sene A, Kamusu-Foguem B, Rumeau P. Telemedicine framework using case-based reasoning with evidences. Comput Methods Programs Biomed 2015; 121 (1): 21–35.
13. Denekamp Y, Peleg M. TiMeDDx—a multi-phase anchor-based diagnostic decision-support model. J Biomed Inform 2010; 43 (1): 111–24.
14. Shen Y, Colloc J, Jacquet-Andrieu A, et al. Emerging medical informatics with case-based reasoning for aiding clinical decision in multi-agent system. J Biomed Inform 2015; 56: 307–17.
15. Elstein A, Bordage J. Psychology of clinical reasoning. In: Dowie J, Elstein A, eds. Professional Judgment: A Reader in Clinical Decision-Making. New York, NY: Cambridge University Press; 1988.
16. Bennet P, Hughes RG, Surphey M. Clinical reasoning, decisionmaking, and action: thinking critically and clinically. In: Hughes RG, ed. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
17. Gruber TR. A translation approach to portable ontology specification. Knowl Acquis 1993; 5 (2): 199–220.
64. Abidi SR, Abidi SS, Hussain S, et al. Ontology-based modeling of clinical practice guidelines: a clinical decision support system for breast cancer follow-up interventions at primary care settings. *Stud Health Technol Inform* 2007; 129 (Pt 2): 845–9.

65. Fox J, Alabassi A, Black E, et al. An ontological approach to modelling tasks and goals. *Stud Health Technol Inform* 2004; 101: 31–45.

66. Achour SL, Dojat M, Rieux C, et al. A UMLS-based knowledge acquisition tool for rule-based clinical decision support system development. *J Am Med Inform Assoc* 2001; 8 (4): 351–60.

67. Wheeler TS, Vallis TM, Giacomantonio NB, et al. Feasibility and usability of an ontology-based mobile intervention for patients with hypertension. *Int J Med Inform* 2018; 119: 8–16.

68. Kostopoulos K, Chouvarda I, Kourtikas V, et al. An ontology-based framework aiming to support personalized exercise prescription: application in cardiac rehabilitation. In: 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society; 2011: 1567–70.

69. Schulz S, Martínez-Costa C. How ontologies can improve semantic interoperability in health care. In: Riaño D, Lenz R, Misk S, Peleg M, Reichert M, ten Teije A, eds. *Process Support and Knowledge Representation in Health Care. ProHealth 2013*, KRAHC 2013. Lecture Notes in Computer Science. Cham, Switzerland: Springer; 2013: 8268.

70. Daughton AR, Priedhorsky R, Fairchild G, et al. An extensible framework and database of infectious disease for biosurveillance. *BMC Infect Dis* 2017; 17 (1): 549.

71. Rospocher M, Serafini L. Ontology-centric decision support. In: proceedings of the 2012 International Conference on Semantic Technologies Meet Recommender Systems and Big Data; 2012: 61–72.

72. Hripcsak G, Johnson SB, Clayton PD. Desperately seeking data: knowledge base-database links. In: proceedings of the Annual Symposium on Computer Applications in Medical Care; 1993: 639–43.

73. Cimino JJ. Putting the “why” in EHR: capturing and coding clinical cognition. *J Am Med Inform Assoc* 2019.

74. Turing AM. Computing machinery and intelligence. *Mind* 1950; 49: 433–60.