Journal of the American Medical Informatics Association, 27(12), 2020, 1968–1976
doi: 10.1093/jamia/ocaa200
Advance Access Publication Date: 29 October 2020
Review

Review

A scoping review of clinical decision support tools that generate new knowledge to support decision making in real time

Anna Ostropolets[1], Linying Zhang[1], and George Hripcsak[1,2]

[1]Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, New York, USA and [2]NewYork-Presbyterian Hospital, New York, New York, USA

Corresponding Author: Anna Ostropolets, MD, Columbia University, 622 West 168th Street, PH-20, New York, NY, USA; ao2671@cumc.columbia.edu

Received 6 April 2020; Revised 24 July 2020; Editorial Decision 29 July 2020; Accepted 4 August 2020

ABSTRACT

Objective: A growing body of observational data enabled its secondary use to facilitate clinical care for complex cases not covered by the existing evidence. We conducted a scoping review to characterize clinical decision support systems (CDSSs) that generate new knowledge to provide guidance for such cases in real time.
Materials and Methods: PubMed, Embase, ProQuest, and IEEE Xplore were searched up to May 2020. The abstracts were screened by 2 reviewers. Full texts of the relevant articles were reviewed by the first author and approved by the second reviewer, accompanied by the screening of articles' references. The details of design, implementation and evaluation of included CDSSs were extracted.
Results: Our search returned 3427 articles, 53 of which describing 25 CDSSs were selected. We identified 8 expert-based and 17 data-driven tools. Sixteen (64%) tools were developed in the United States, with the others mostly in Europe. Most of the tools (n = 16, 64%) were implemented in 1 site, with only 5 being actively used in clinical practice. Patient or quality outcomes were assessed for 3 (18%) CDSSs, 4 (16%) underwent user acceptance or usage testing and 7 (28%) functional testing.
Conclusions: We found a number of CDSSs that generate new knowledge, although only 1 addressed confounding and bias. Overall, the tools lacked demonstration of their utility. Improvement in clinical and quality outcomes were shown only for a few CDSSs, while the benefits of the others remain unclear. This review suggests a need for a further testing of such CDSSs and, if appropriate, their dissemination.

Key words: evidence-based medicine, clinical decision support system, electronic health records, observational data

INTRODUCTION

Since the 1990s, when the concept of evidence-based medicine was first introduced, it has become the leading paradigm in clinical practice, shaping the way we view medicine today. Accumulated scientific evidence informs clinical decisions to reach optimal care, improve patient outcomes, and reduce costs.[1–3] Moreover, evidence-based practice, as opposed to intuitive care, allows reliable intervention comparison.[4]

Nevertheless, medical evidence is neither comprehensive nor precise. Randomized clinical trials (RCTs), which are the backbone of medical evidence, have pitfalls and biases. Owing to an inherited tradeoff between accuracy and generalizability, RCTs are oftentimes not applicable to real-world patients.[5]

Many of them consider only a subset of the population, excluding patients with advanced cancer, patients with chronic kidney disorder or systemic disorders, the elderly, pregnant women, and other vulnerable populations.[6,7] Clinical trials also tend to focus narrowly on one condition at a time, which produces recommendations that are entirely relevant to a patient with a single disorder and rarely provide clear guidance for patients with multiple conditions[7,8] or complex interventions.[9–11] As trials are expensive and time-consuming, large-scale clinical trials may not be readily available for new drugs or rare disorders.[12,13] When current evidence fails to provide guidance for the previous scenarios, clinicians have to rely on their limited experience.

However, a growing body of observational data, along with the continuing accumulation of practice-based evidence, has made new approaches to evidence generation available.[3,14,15] Observational studies have a potential to inform clinical decision making by generating and disseminating new knowledge across medical community,[16] but they are also time-consuming. There are new clinical decision support systems (CDSSs) that generate new knowledge in real time.[17] While the more traditional rule-based systems are developed using existing clinical knowledge and can only provide recommendations for a limited number of cases,[18] these CDSSs have a potential to address a broad range of clinical questions in a timely manner. It is unclear, though, to what extent such CDSSs inform decision making at the bedside.[16] Moreover, a comprehensive review of such CDSSs, their design, capacities and impact is lacking. We conducted a scoping[19] review of CDSSs that use patient data for generating new knowledge to assist with complicated clinical cases, and examined their adoption and impact on decision making and patient outcomes.

MATERIALS AND METHODS

Search strategy

We conducted a scoping review, including the use of a formal search strategy, appraisal of study quality, and a narrative synthesis of findings. To inform our analysis, we performed a systematic search of 4 databases (PubMed, Embase, ProQuest, and IEE Xplore) for articles published in English before May 22, 2020.

The focused question that drove this review was, "What are the features and impact of clinical decision support tools that generate new knowledge to address complex clinical cases not covered by the existing evidence?" To answer this question, we identified 4 components of our search:

1. Electronic health records (EHRs)
2. Clinical decision support tools

   We began with browsing available literature to identify terms that can be used for article retrieval. After having found that the articles of interest included disparate keywords (eg, CDSSs, health service, prototype), together with librarians we expanded the list of our search terms to achieve better coverage (the detailed search strategy can be found in Supplementary Appendix A).
3. Evidence-based medicine

   We included the hyponyms and synonym terms for evidence-based medicine, including broader concepts (evidence and decision making) to obtain all relevant results.
4. Complex clinical cases

   Based on the previous literature,[20–26] we included not only the terms representing complicated cases, but also additional terms such as "polypharmacy," "comorbidity," "patient like mine," "patient-related questions," and others (Supplementary Appendix A).

The search terms included MeSH (Medical Subject Headings) concepts (PubMed), Emtree (Embase), and free-text terms, combining the 4 groups of terms described above.

Inclusion and exclusion criteria

We included articles that described any type of clinical decision support system, which was defined as any computer system designed to impact clinician decision making about individual patients at the point in time that these decisions are made,[27] that use patient data to address clinical questions not covered by existing evidence and are designed to be used by clinicians. We focused on those CDSSs that either modify existing evidence, tailoring it to the patient of interest or generate previously unknown knowledge to facilitate decision making. Thus, this article does not include CDSSs that use existing guidelines, clinical trials, or literature as is.

We excluded articles meeting any of the following criteria:

1. The CDSSs only used existing evidence (clinical trials, guidelines, published literature)
2. The study was in a language other than English
3. The study used data other than clinical (eg, genomic or protein data) or simulated datasets

While review articles were excluded from the review itself, they were used to obtain relevant references and to inform this discussion.

Study selection and data synthesis

Two reviewers (A.O. and L.Z.) independently screened the title and abstract for each study for inclusion and exclusion criteria. The level of agreement between the 2 reviewers was assessed by a Cohen's kappa score. Disagreements between the 2 reviewers were resolved by discussion until consensus was reached. The list of studies selected for full text review was screened for relevant references. A.O. reviewed the full text of the selected studies and further excluded irrelevant studies. For each tool, we extracted the year of its implementation or evaluation, the site of intervention, its main area (specialty), focus (patient care, research, quality improvement), methods used, evaluation type and evaluation outcomes. Additionally, a manual search was conducted to identify other articles describing included CDSSs. Extracted data were reviewed and approved by L.Z.

RESULTS

We retrieved 3427 articles, of which 172 articles were potentially relevant based on abstract, title, and keywords screening. A total of 144 articles were identified as duplicates and removed. The level of agreement between the 2 reviewers was reflected by a Cohen's kappa of 0.84.We additionally found 83 articles through reference lists. 53 manuscripts describing 25 CDSSs were selected for this review. Figure 1, following the PRISMA (Preferred Reporting Items for Systematic Reviews

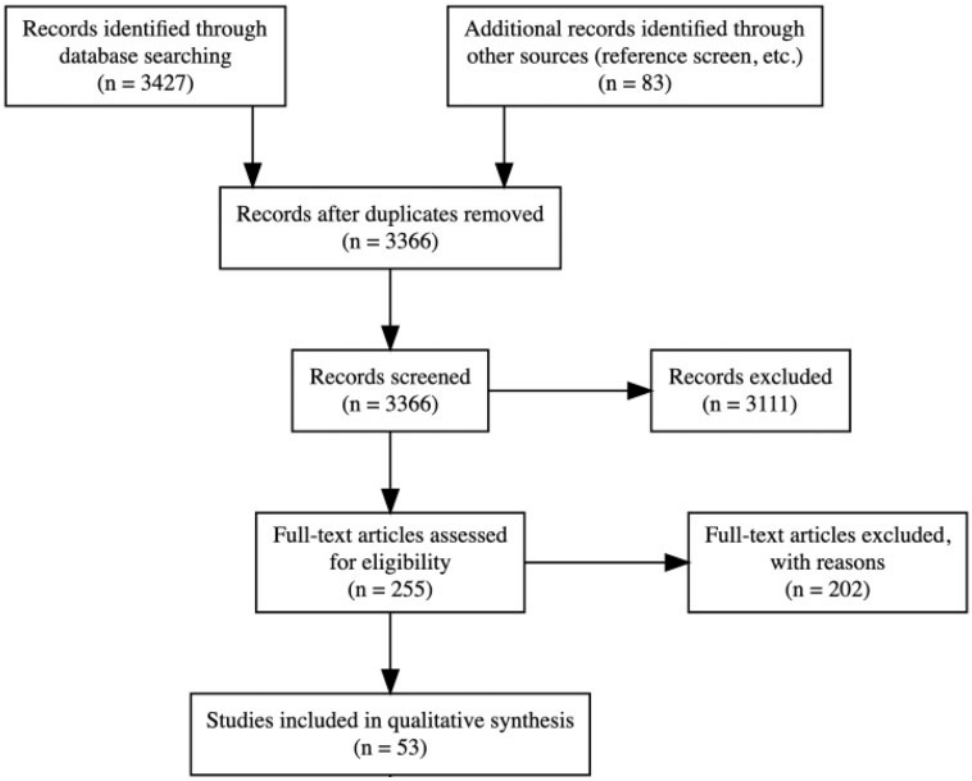

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart for the article selection and review.

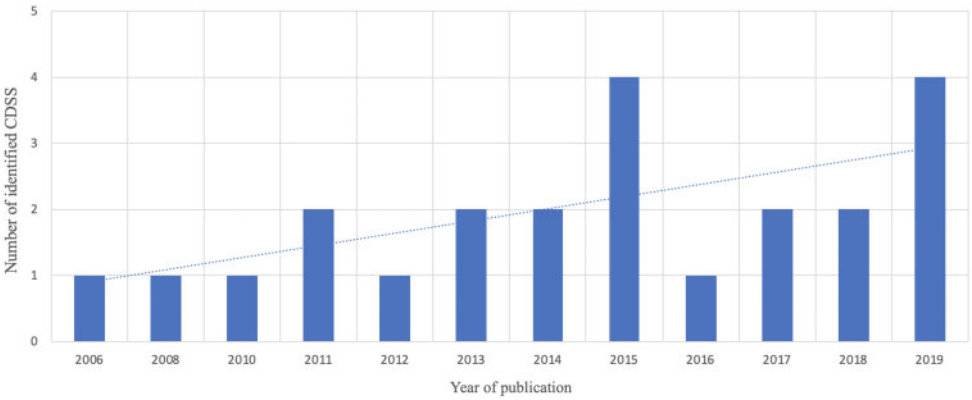

Figure 2. Temporal trend in development of tools described in this study. CDSS: clinical decision support system.

and Meta-Analyses) reporting standards, summarizes the article selection process and its results.

The number of tools peaked in 2015 and 2019 (Figure 2). Only 36% (n = 9) of them were implemented in more than 1 site with 64% (n = 16) of the tools developed in the United States, the others—in Europe (n = 6), the United Kingdom (n = 1) or China (n = 2).

While all of the CDSSs included in the study were either used or planned to be used for clinical care, 68% of CDSSs also focused on quality of care or research (n = 8 [32%] and n = 9 [36%] respectively) (Supplementary Appendix B). Oncology was the main area of use (9 CDSSs, 36%) followed by surgery, psychiatry, and internal medicine (n = 2, 8% each). The other tools did not have a specific area of use, albeit specific use cases were used to show the features of some prototypes (potentially unrestricted) (Supplementary Appendix B). Only 40% (10) of the tools were deployed and used in practice.

The tools in this review can be classified into 2 groups based on the main approach used to infer new knowledge: (1) data-driven tools, which use patient data to generate practice-based evidence[18] in real time; and (2) expert-based tools, which require experts to incorporate practice-based evidence into algorithms subsequently used in CDSSs. Both of these groups produce knowledge that does not explicitly exist outside of CDSSs and should be useful for decision making for a patient of interest. Based on the analytical component, data-driven tools can further be classified into (1) visual non–analytics-based tools and (2) analytics tools (Table 1).

Table 1. Included articles grouped by the inference mechanism and analytical component

Group	Sub-group	Included CDSSs
Data-driven CDSSs (n = 17)	Visual non–analytics-based tools (n = 6)	"Composer," "ePEPS," "CaVa," "CareFlow," "Patient-like-mine," "PatternFinder"
	Analytics tools (n = 11)	"Care Pathway Workbench," "Green Button," "CoCo," "VisualDecisionLinc," "Melanoma Rapid Learning Utility," "DICON," CDSSs for radiologists (Morrison et al),[37] 2 CDSSs for prostate cancer (Bernard et al),[42] 2 CDSSs for diabetes mellitus and acute coronary syndrome (Xia et al)[47,48]
Expert-based CDSSs (n = 8)		"MayoExpert," "e-bipolar," ROAD2H CDSSs, "Oncology Expert Advisor," "P4 Pathways," "Level I Pathways," "ViaOncology," "eviti"

CDSS: clinical decision support system.

Data-driven tools

Visual non–analytics-based tools

Visual non–analytics-based tools allow defining patients based on the criteria of interest, aggregating them according to a set of rules defined by a clinician and visually inspecting resulting patient cohorts. Individual patient data or aggregated data can be aligned by timeline and presented to a clinician for comparison. With rare exceptions,[28] they do not require a third party to perform an analysis: clinicians can obtain relevant information on their own. Patient criteria can be selected from a predefined list[28,29] or from any structured data in the EHR system.[30] The latter increases the variety of questions clinician can ask as any diagnosis, procedure, or laboratory test from the EHR system can be selected. While such tools are not capable of generating gold-standard evidence, they allow clinicians to learn from previous care, observe, and compare patient outcomes.

One of the tools, PatternFinder,[31–35] visualizes patient records according to temporal queries and allows specifying an index event and 2 additional events only (Figure 3B). Visualization is limited to matched events, so that clinicians can only explore the common events but not those that differ among patients. The authors performed extensive 4-month usability testing for patients with contrast nephropathy.

CaVa[28] visually represents the changes in the predefined variables of interest through line thickness, where lines connect clinical events and are aligned by timeline. As opposed to PatternFinder, it does not limit the number of events to display but requires the study team to identify patients and select variables in advance. A prototype, developed for cardiology patients, could also support similarity measurements and utilization analysis. CareFlow,[36] developed independently, has a similar interface and features (Figure 3C). It was similarly tested for cardiology patients (congestive heart failure).

A CDSS for radiologists presented by Morrison et al[37] aims at identifying patients with similar demographic and lung cancer-related characteristics. It displays descriptive statistics, mainly focusing on cancer characteristics, and unlike the other tools, it is characterized by limited visualization. Another distinctive feature is repurposing of a lung screening trial data set, which limits its ability to learn from the new patient data.

Similarly to the previous tool, Composer[29] was developed for a single specialty, assisting orthopedic surgeons in assessing patient state after spinal procedures. The developers prespecified outcome measures and subsequently plotted them for individual patients or aggregated cohorts (Figure 3D). As the tool has recently been developed, we have no information about its evaluation.

The ePEPS toolbox[30,38,39] was built on top of the nationwide French EHR database, leveraging the benefits of linking patient data across multiple institutions. It supports constructing patient cohorts based on all available structured data, not limiting variables to a predefined set. Clinicians can then compare the cohorts based on geographic distribution, explore the distribution of the events of interest across groups, and inspect patient trajectories.

A tool presented by Li et al[40] used elastic search to search for patients of interest in real time. The tool preserves the ability to transparently explore "what-if" scenarios for cohorts of patients. It is achieved by comparing the trajectory of a given person to the trajectories of similar patients and visually analyzing if his or her trajectory is within normal bounds.

Analytics tools

Analytics tools aggregate patient data and use statistical approaches to compare patient cohorts. Data analysis can vary from simple descriptive statistics to comparative effectiveness studies, but generally allows not only learning from previous patient care, but also reliably comparing patient outcomes and characteristics. The tools described in this section mainly differ in the methods used to obtain cohorts and the ways results are presented to clinicians.

We start with the tools that combine visual representation of patient cohorts with statistical analysis that allows clinicians to obtain estimates (odds ratios or relative risk) for the groups of interest.

CoCo,[41] which stands for Cohort Comparison, provides visualization of interactively refined patient cohorts as well as individual patient records as time sequences (Figure 3A). Clinicians can then compare the cohorts using formal statistical approaches (survival analysis and log-rank test).

Bernard et al[42] developed a dashboard similar to CoCo to visualize multiple patient trajectories for patients with prostate cancer. Clinicians can select patients and compute correlations between variables and a patient cohort. Patient histories are synchronized, and each history is shown as a line with a color corresponding to a phase of prostate cancer treatment. The

Figure 3. Snapshots of visual tools described in this study: (A) CoCo, (B) PatternFinder, (C) CareFlow, and (D) Composer. Permissions for image reuse were obtained from the authors of the tools.

authors further explored this area by developing dashboard networks to allow cohort comparison.[43] To conduct user acceptance testing, Barnard et al asked clinicians to run an observational study using the prostate cancer dashboard. They showed that the system increased the efficiency of analytics and provided visual assistance for complicated temporal relationships in the data. Malik et al[41] took the same evaluation approach for CoCo and generated use cases to access perceived usefulness of the tool in emergency department settings.

Melanoma Rapid Learning Utility (MLRU)[44] and VisualDecisionLinc[45] similarly enable physician-driven cohort selection and comparative effectiveness analysis for melanoma and major depressive disorder, respectively. Physicians construct cohorts based on demographic data, drug exposure data, and melanoma-related variables (MLRU), and can subsequently inspect odds ratios of outcomes produced by survival analysis. MLRU underwent user acceptance testing, with positive feedback and physicians more interested in using it for research purposes. It was deployed, but the actual use of the tool is unknown.

Cao et al[46] used a glyph-based visualization system (DICON) to show structured data from patients' EHR and compute similarity scores across patient data elements. The tool calculates the correlation between selected features (eg, International Classification of Diseases–Tenth Revision–Clinical Modification codes) and the cluster of similar patients. The authors conducted a formal mixed (qualitative and quantitative) user acceptance testing with domain experts and nonexperts focusing on the design of the icons that represented patient cohorts. They found that their design provided higher efficiency on group comparison; they provided limited information about user feedback.

Xia et al[47,48] developed 2 separate prototypes that use clustering techniques to identify patient subgroups within a disorder (acute coronary syndrome and diabetes mellitus). Upon clinical encounter, a clinician can see a cluster of patients who are similar to the patient of interest and inspect their characteristics, including demographics, disease onset and progression, drug exposure, and outcomes.

As opposed to visual analytics-based tools, Green Button[17,49,50] presents cohort comparison in the form of reports that the developers supply to clinicians. Developed primarily for clinical care, it leverages observational studies to answer clinical questions ranging from simple descriptive statistics to comparative effectiveness studies. A fast search engine retrieves patients of interest and visualizes their medical events as temporal sequences, allowing fast and efficient iterations. This is the only tools that mitigates confounding (propensity score matching) in addition to survival analysis, incidence rates, or descriptive statistics. Compared with the other tools described here, clinicians have to supply their questions to the study team and cannot execute analysis on their own. The CDSSs delivers reports through protected email and phone conversations, rather than through a standalone user interface.

The last tool in this section, Care Pathway Workbench,[51] transitions from pure data-driven approaches to integration of newly generated real practice evidence into existing care pathways. It uses hidden Markov Models to identify the deviations of real practice from clinical guidelines and mines EHR data to obtain clinical event sequences. It then presents these insights from real-world practice to clinicians so that they can modify care plans for a specific patient.

Expert-based (knowledge-aggregative) tools

Expert-based CDSSs rely on a study team (usually a multidisciplinary clinical team) to synthesize multiple sources of evidence into a knowledge base incorporating evidence-based recommendations and local insights of previous patient care and outcomes. Similarly to the traditional rule-based CDSSs, such tools use an existing evidence knowledge base complemented by the newly generated practice-based evidence, which is not available outside of the tool.

A significant portion of the tools presented in this group relates to cancer care. The latter is characterized by multiple "best" treatments that accommodate specific patients' characteristics. Such treatments or pathways are often selections of the most cost-effective treatments and are developed collaboratively with local specialists. P4 Pathways,[52–54] ViaOncology,[55,56] Level I Pathways,[57–63] and eviti[64,65] have been widely adopted across the United States. They aggregate and modify cancer clinical guidelines according to the community-based practices and practice-based evidence so that these human-curated pathways reflect the way care is delivered. These tools can be used to query EHR data and obtain the cohorts of similar patients for whom specific pathways are applicable.

On the one hand, disadvantages of such tools include sensitivity to incomplete data, dependence on local experts and previous practices, and focus on treatment cost. On the other hand, they have established feedback loops for fast evidence modification on practices changes, or new knowledge becomes available. As treatment pathways are curated by the leaders in the field, they can be perceived as trustworthy, which may have facilitated their adoption.[66]

Pathway-related tools underwent extensive evaluation, including patient and quality outcomes. Level I Pathways was made available to the clinicians within the U.S. Oncology Network (a network of more than 400 integrated, community-based oncology practices) in 2013 and was proven to reduce costs of treatment for patients with lung, breast and colorectal cancer; reduce duration of treatment; and lower cancer-related re-admission rates.[57,59] Nevertheless, no statistically significant difference in survival rates was found. P4 Pathways reduced inpatient admission rate and duration of therapy for chronic lymphocytic leukemia.[53] ViaOncology showed the same results for metastatic colorectal cancer.[56]

Oncology Expert Advisor[67] is a closely related CDSS that also provides pathway-like recommendations related to cancer care. While it also aggregates multiple sources of evidence, the core function of this tool is to promote sharing best practices by incorporating peer-to-peer consultations based on the patient profile created by this tool. It subsequently includes the advice management system that allows consultation tracking.

ROAD2H[68,69] and MayoExpert[70] are 2 other practice-based evidence learning health systems, which aggregate recommendations from international, national, local guidelines, and institutional practices to provide tailored knowledge. ROAD2H uses argumentation with a clear provenance trail to resolve conflicting recommendations, while MayoExpert represents care models as sequence of nodes, in which a node is a decision point. They provide clinicians with a patient-specific recommendation based on hospital EHR data prioritizing institutional best practices. ROAD2H has been piloted in 2 sites and currently provides recommendations for patients with chronic obstructive pulmonary disorder and chronic kidney failure. MayoExpert, on the other hand, incorporated 106 models at the time of publication and was used by 60% of clinicians at the Mayo Clinic sites. The authors found that general practice specialists and less experienced practitioners used the tool more often than specialists and more experienced clinicians.

The application e-bipolar[71] stands on its own in this review. As opposed to the "top-down" approach used by pathway-related tools, e-bipolar emphasizes providing reliable assessments of patients with bipolar disorder. Under this initiative, participating French practices can assess their patients and get a comprehensive patient review including personalized treatment strategy. The coordinating center manages assessments, provides guidance on optimal treatment, and shares practice-based evidence by providing anonymized data through e-bipolar.

DISCUSSION

In this study, we explored the tools that aim at guiding clinicians in complicated clinical cases for which they do not have gold-standard evidence. Existing reviews focus on the tools that facilitate evidence-based practices, but the latter cannot answer all questions outside of guidelines or trials.[72–74] Meanwhile, the availability of knowledge plays an important role in the quality of decision making (Figure 4).[75–77] For questions not covered by existing evidence, clinicians must rely on their limited experience. For example, there is no clear consensus on common clinical questions like, "Should a diabetic patient on angiotensin-converting enzyme (ACE) inhibitors, diuretics and sodium glucose co-transporter 2 (SGLT2) inhibitors be taken off diuretics as SGLT2 inhibitors act as diuretics?" which results in clinical practice variation.

Among other solutions, CDSSs can generate additional knowledge to guide clinicians. They vary in approaches, target audience, level of flexibility and automation, and are at different stages of adoption. Nevertheless, they all share the main feature: they produce new knowledge by either generating new evidence or adjusting and personalizing the existing one.

Visual tools focusing at presenting longitudinal patient data has been known for a long time, starting with LifeLines[78] and KNAVE.[79] They evolved in 2 directions: (1) adding more sophisticated features to individual views and (2) aggregating patient data into groups with a subsequent visual or statistical analysis. The main highlights of visual systems are automated process, fast execution, flexibility, relatively small maintenance cost, and intuitive representation of the results. On the one hand, an ability to quickly explore aggregated patient data facilitates fast answers to clinical questions in real time. It also means that tool utilization is relatively cheap as it does not rely on a team supporting query execution and report generation. On the other hand, it demands familiarity with the data, which can be unfeasible for nonexperienced clinicians. Additionally, such tools are inferior to analytic CDSSs in terms of scientific rigor, as they do not imply that observed differences in patient cohorts are statistically significant or unbiased.[80]

Another approach, implemented in CaVa, Green Button, and expert-based CDSSs, requires a third party (study team or experts) to generate knowledge either by running small-scale observational studies on patient data or incorporating new practice-based evidence into personalized recommendations. An advantage of such approach is involvement of skilled pro-

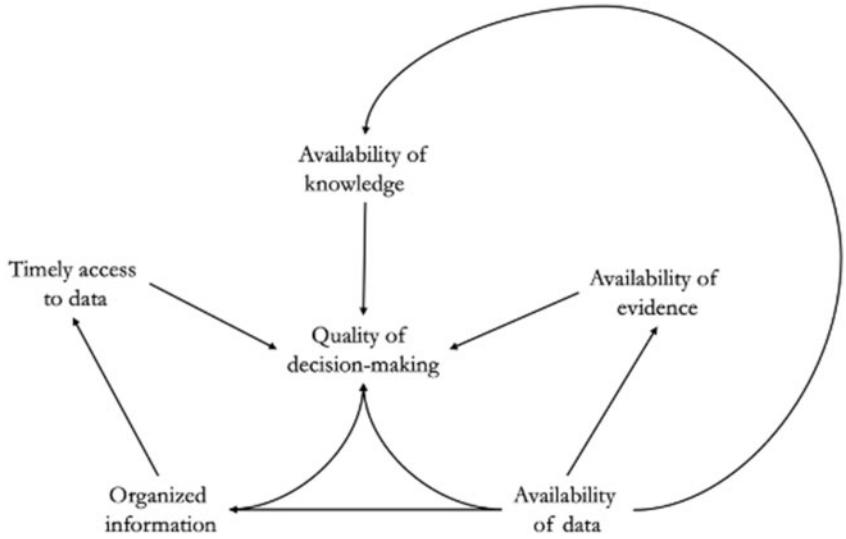

Figure 4. Factors influencing the quality of decision making through a causal-loop diagram.

fessionals, who are familiar with the data and research methods. In expert-based tools, the knowledge has to be gathered in advance and then tailored to patient's characteristics. New knowledge, therefore, cannot readily be made available if complicated clinical scenarios are not covered by the existing pool of care models. As timely answers can be critical in decision making, another approach adopted by Green Button is to run observational studies in real time. On the one hand, while it can address a broader spectrum of questions in a timely manner, such a type of CDSS must rely on efficient communication with clinicians in order to capture additional details and refine questions. On the other hand, such CDSSs have a potentially broader audience since they do not require specific skills or knowledge and the results can be interpreted by skilled personnel or introduced in a simplified form in the reports.

Regardless of knowledge inference methods, CDSSs for new evidence generation were mainly developed and implemented at one site and rarely disseminated. Data-driven tools used the local EHR data, and there mostly the structured (mainly International Classification of Diseases revisions; Current Procedural Terminology, Fourth Edition; and Anatomical Therapeutic Chemical Classification) data. Unstructured data was processed by only 2 tools,[40,81,82] but none of the tools harmonized data from disparate data sources or used common data models.[83] Lack of data standardization can pose a challenge if generating knowledge requires gathering data from multiple sites or sources, for example, if a disorder or event is rare.

Lack of evaluation is another finding in our study. For some of the tools, there was no information about evaluation including the types of tests that should be performed at the initial stages. The pathway-related group was the only group for which an impact on patient and quality outcomes has been shown. These CDSSs are based on pathways supported by payors,[52] which may be a reason for their wide adoption and evaluation. Another possible reason may be expert involvement.

As long as traditional RCTs cannot deliver sufficient evidence in a timely manner, such tools may be a good alternative to disparate intuitive clinical practices. Due to the limitations of the current tools, new robust CDSSs may be needed. They should build on previous designs and incorporate their strength in delivering new evidence at the point of care. Ease of use and intuitive result presentation should be combined with robust statistical methods and phenotyping. While full-scale observational studies usually undergo rigorous assessment,[14,15]small-scale real-time studies may not produce unbiased estimates. For example, rule-based phenotyping with chart review validation[84] may not be feasible in real time, which creates a need for best practices for fast yet accurate patient identification. If a tool aims to answer questions from different areas or specialties, the ability of a particular data source to supply accurate data should be articulated to clinicians and any data quality issues or other limitations should be acknowledged. If phenotyping is done by an individual other than the end user, phenotyping principles, accuracy, and limitations should be transparently described as well. Regardless of the design used, a CDSS has also to be seamlessly integrated in the workflow. Finally, the impact of such CDSSs on decision making, quality, and patient outcomes should be evaluated.

CONCLUSION

We found 25 CDSSs that can generate new knowledge for complicated clinical cases in the absence of existing evidence, although only 1 analytic tool addressed confounding and bias. Most of the tools were data-driven and accompanied by expert-based (knowledge aggregative) tools. Overall, evidence regarding their effectiveness was lacking. Positive improvement on clinical and quality outcomes were shown only for a limited number of interventions, while the benefits from the others remain unclear. This review suggests that there is a need for a further testing of CDSSs and, if appropriate, dissemination.

FUNDING

This work was supported by the National Institutes of Health grant R01 LM006910 (to AO, LZ, and GH).

AUTHOR CONTRIBUTIONS

AO designed the review, search strategy, and conducted database searches. AO and LZ conducted article screening, data analysis, and interpretation. GH oversaw the study design and execution. All authors reviewed the content.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

REFERENCES

1. Sackett DL, Rosenberg WMC, Gray JAM, *et al*. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312 (7023): 71–2.
2. Timmermans S, Mauck A. The promises and pitfalls of evidence-based medicine. *Health Aff (Millwood)* 2005; 24 (1): 18–28.
3. Chow N, Gallo L, Busse JW. Evidence-based medicine and precision medicine: complementary approaches to clinical decision-making. *Precis Clin Med* 2018; 1 (2): 60–4.
4. Bahtsevani C, Udén G, Willman A. Outcomes of evidence-based clinical practice guidelines: A systematic review. *Int J Technol Assess Health Care* 2004; 20 (4): 427–33.
5. Glasgow RE, Green LW, Klesges LM, *et al*. External validity: we need to do more. *Ann Behav Med* 2006; 31 (2): 105–8.
6. Van Spall HGC, Toren A, Kiss A, *et al*. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* 2007; 297 (11): 1233–40.
7. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet* 2005; 365 (9453): 82–93.
8. Boyd CM, Vollenweider D, Puhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. *PLoS One* 2012; 7 (8): e41601.
9. Marchal B, Westhorp G, Wong G, *et al*. Realist RCTs of complex interventions – an oxymoron. *Soc Sci Med* 2013; 94: 124–8.
10. Schmidt AF, Groenwold RHH, van Delden JJM, *et al*. Justification of exclusion criteria was underreported in a review of cardiovascular trials. *J Clin Epidemiol* 2014; 67 (6): 635–44.
11. Ely JW, Osheroff JA, Ebell MH, *et al*. Analysis of questions asked by family doctors regarding patient care. *BMJ* 1999; 319 (7206): 358–61.
12. Bell SA. Tudur Smith C. *A Comparison of Interventional Clinical Trials in Rare versus Nonrare Diseases: An Analysis of Clinicaltrials.gov*. Orphanet J Rare Dis 2014; 9 (1): 170–81.
13. Griggs RC, Batshaw M, Dunkle M, *et al*. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab* 2009; 96 (1): 20–6.
14. Visvanathan K, Levit LA, Raghavan D, *et al*. Untapped potential of observational research to inform clinical decision making: American Society of Clinical Oncology Research Statement. *J Clinc Oncol* 2017; 35 (16): 1845–54.
15. Dreyer NA, Tunis SR, Berger M, *et al*. Why observational studies should be among the tools used in comparative effectiveness research. *Health Aff (Millwood)* 2010; 29 (10): 1818–25.
16. Frieden TR. Evidence for health decision making—beyond randomized, controlled trials. *N Engl J Med* 2017; 377 (5): 465–75.
17. Gombar S, Callahan A, Califf R, *et al*. It is time to learn from patients like mine. *NPJ Digit Med* 2019; 2 (1). doi : 10.1038/s41746-019-0091-3
18. Middleton B, Sittig DF, Wright A. Clinical decision support: a 25 year retrospective and a 25 year vision. *Yearb Med Inform* 2016; 25 (S1): S103–16.
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005; 8 (1): 19–32.
20. Aakre CA, Maggio LA, Fiol GD, Cook DA. Barriers and facilitators to clinical information seeking: a systematic review. *J Am Med Inform Assoc* 2019; 26 (10): 1129–40.
21. Covell DG, Uman GC, Manning PR. Information needs in office practice: are they being met? *Ann Intern Med* 1985; 103 (4): 596–9.
22. Song M, Spallek H, Polk D, Schleyer T, Wali T. How information systems should support the information needs of general dentists in clinical settings: suggestions from a qualitative study. *BMC Med Inform Decis Mak* 2010; 10 (1): 7.
23. Forsythe DE, Buchanan BG, Osheroff JA, Miller RA. Expanding the concept of medical information: an observational study of physicians' information needs. *Comput Biomed Res* 1992; 25 (2): 181–200.
24. Gorman P. Information needs in primary care: a survey of rural and nonrural primary care physicians. *Stud Health Technol Inform* 2001; 84 (1): 338–42. doi : 10.3233/978-1-60750-928-8-338.
25. Green ML, Ciampi MA, Ellis PJ. Residents' medical information needs in clinic: are they being met? *Am J Med* 2000; 109 (3): 218–23.
26. Bright TJ, Wong A, Dhurjati R, *et al*. Effect of clinical decision-support systems: a systematic review. *Ann Intern Med* 2012; 157 (1): 29–43.
27. Berner ES. *Clinical Decision Support Systems*. 2nd ed. New York, NY: Springer; 2007.
28. Zhang Z, Gotz D, Perer A. Iterative cohort analysis and exploration. *Inform Vis* 2015; 14 (4): 289–307.
29. Rogers J, Spina N, Neese A, *et al*. Composer—visual cohort analysis of patient outcomes. *Appl Clin Inform* 2019; 10 (02): 278–85.
30. Happe A, Drezen E. A visual approach of care pathways from the French nationwide SNDS database - from population to individual records: the ePEPS toolbox. *Fundam Clin Pharmacol* 2018; 32 (1): 81–4.
31. Plaisant C, Lam S, Lam SJ, *et al*. Searching electronic health records for temporal patterns in patient histories: a case study with Microsoft Amalga. *AMIA Annu Symp Proc* 2008; 2008: 601–5.
32. Fails J, Karlson A, Shahamat L, *et al*. A visual interface for multivariate temporal data: finding patterns of events across multiple histories. In: proceedings of 2006 IEEE Symposium On Visual Analytics and Technology; 2006: 167–74.
33. Lam S, Shneiderman B. *PatternFinder in Microsoft Amalga: Temporal Query Formulation and Result Visualization in Action*. College Park, MD: University of Maryland; 2008.
34. Song H, Brennan J, Negahban N. *PatternFinder 2.0: Usability Test and Redesign of a Patient History Search System*. College Park, MD: University of Maryland; 2005.
35. Ayewah N, Johnson G, Song H. *Patternfinder 3.0: Sparse Temporal Data Visual Query Application*. College Park, MD: University of Maryland; 2011.
36. Perer A, Gotz D. Data-driven exploration of care plans for patients. In: Mackay W, ed. *CHI '13 Extended Abstracts on Human Factors in Computing Systems on - CHI EA '13*. Paris, France: ACM Press; 2013: 439.doi : 10.1145/2468356.2468434
37. Morrison JJ, Hostetter J, Wang K, *et al*. Data-driven decision support for radiologists: re-using the National Lung Screening Trial dataset for pulmonary nodule management. *J Digit Imaging* 2015; 28 (1): 18–23.
38. Drezen E, Guyet T, Happe A. From medico-administrative databases analysis to care trajectories analytics: an example with the French SNDS. *Fundam Clin Pharmacol* 2018; 32 (1): 78–80.
39. Scailteux L-M, Droitcourt C, Balusson F, *et al*. French administrative health care database (SNDS): the value of its enrichment. *Therapies* 2019; 74 (2): 215–23.
40. Li P. Yates SN. Lovely JK. et al. Patient-like-mine: A real time, visual analytics tool for clinical decision support. In: proceedings of 2015 IEEE International Conference on Big Data (Big Data); 2015: 2865–7; Santa Clara, CA. doi : 10.1109/BigData.2015.7364104.
41. Malik S, Du F, Monroe M, *et al*. Cohort comparison of event sequences with balanced integration of visual analytics and statistics. In: proceedings of the 20th International Conference on Intelligent User Interfaces - IUI '15; 2015: 38–49.
42. Bernard J, Sessler D, May T, *et al*. A visual-interactive system for prostate cancer cohort analysis. *IEEE Comput Grap Appl* 2015; 35 (3): 44–55.
43. Bernard J, Sessler D, Kohlhammer J, *et al*. Using dashboard networks to visualize multiple patient histories: a design study on post-operative prostate cancer. *IEEE Trans Visual Comput Graphics* 2019; 25 (3): 1615–28.

44. Finlayson SG, Levy M, Reddy S, *et al.* Toward rapid learning in cancer treatment selection: An analytical engine for practice-based clinical data. *J Biomed Inform* 2016; 60: 104–13.
45. Mane KK, Bizon C, Schmitt C, *et al.* VisualDecisionLinc: a visual analytics approach for comparative effectiveness-based clinical decision support in psychiatry. *J Biomed Inform* 2012; 45 (1): 101–6.
46. Cao N, Gotz D, Sun J, *et al.* DICON: interactive visual analysis of multidimensional clusters. *IEEE Trans Vis Comput Graph* 2011; 17: 2581–90.
47. Xia E, Liu H, Li J, *et al.* Gathering real world evidence with cluster analysis for clinical decision support. *Stud Health Technol Inform* 2017; 245: 1185–9.
48. Xia E, Wang K, Zhang Y, *et al.* A data-driven clinical decision support system for acute coronary syndrome patient similarity. In: proceedings of 2019 IEEE International Conference on Healthcare Informatics (ICHI); 2019: 1–6.
49. Gallego B, Walter SR, Day RO, *et al.* Bringing cohort studies to the bedside: framework for a 'green button' to support clinical decision-making. *J Comp Effect Res* 2015; 4 (3): 191–7.
50. Schuler A, Callahan A, Jung K, *et al.* Performing an informatics consult: methods and challenges. *J Am Coll Radiol* 2018; 15 (3): 563–8.
51. Yu Y, Liu H, Li J, *et al.* Care pathway workbench: evidence harmonization from guideline and data. *Stud Health Technol Inform* 2014; 205: 23–7.
52. Feinberg BA, Lang J, Grzegorczyk J, *et al.* Implementation of cancer clinical care pathways: a successful model of collaboration between payers and providers. *J Oncol Pract* 2012; 8 (3S): e38s.
53. Nabhan C, Mato AR, Feinberg BA. Clinical pathways in chronic lymphocytic leukemia: challenges and solutions: pathways for CLL. *Am J Hematol* 2017; 92 (1): 5–6
54. Kreys ED, Koeller JM. Documenting the benefits and cost savings of a large multistate cancer pathway program from a Payer's perspective. *J Oncol Pract* 2013; 9 (5): e241–7–e247.
55. Ellis PG. Development and implementation of oncology care pathways in an integrated care network: the via oncology pathways experience. *J Oncol Pract* 2013; 9 (3): 171–3.
56. Ellis PG, O'Neil BH, Earle MF, *et al.* Clinical pathways: management of quality and cost in oncology networks in the metastatic colorectal cancer setting. *J Oncol Pract* 2017; 13 (5): e522–9.
57. Hoverman JR, Klein I, Harrison DW, *et al.* Opening the Black Box: the impact of an oncology management program consisting of level I pathways and an outbound nurse call system. *J Oncol Pract* 2014; 10 (1): 63–7.
58. Hoverman JR, Cartwright TH, Patt DA, *et al.* Pathways, outcomes, and costs in colon cancer: retrospective evaluations in two distinct databases. *J Oncol Pract* 2011; 7 (3S): 52s–9s.
59. Neubauer MA, Hoverman JR, Kolodziej M, *et al.* Cost effectiveness of evidence-based treatment guidelines for the treatment of non–small-cell lung cancer in the community setting. *J Oncol Pract* 2010; 6 (1): 12–8.
60. Hoverman JR, Klein I, Harrison D, *et al.* Impact of an oncology management program using level I pathways, a nurse call system, and advance care planning. *J Clinc Oncol* 2013; 31 (31_suppl): 119.
61. Goldsmith PJ. NCCN's value pathways: the drive for quality cancer care. *J Natl Compr Canc Netw* 2013; 11 (2): 119–20.
62. Kolodziej M, Hoverman JR, Garey JS, *et al.* Benchmarks for value in cancer care: an analysis of a large commercial population. *J Oncol Pract* 2011; 7 (5): 301–6.
63. Espirito JL, Arlen A, Garey JS *et al.* A quality improvement program to increase performance with clinical oncology pathways. *J Clinc Oncol* 2012; 30 (34_suppl): 65.
64. DeMartino JK, Larsen JK. Equity in cancer care: pathways, protocols, and guidelines. *J Natl Compr Canc Netw* 2012; 10 (Suppl_1): S-1–9.
65. Kelly RJ, Forde PM, Elnahal SM, *et al.* Patients and physicians can discuss costs of cancer treatment in the clinic. *J Oncol Pract* 2015; 11 (4): 308–12.
66. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg. E, eds. Clinical Practice Guidelines We Can Trust. Washington, DC: *National Academies Press*; 2011.
67. Simon G, DiNardo CD, Takahashi K, *et al.* Applying artificial intelligence to address the knowledge gaps in cancer care. *Oncologist* 2019; 24 (6): 772–82.
68. Toni F. Argumentation-based clinical decision support system in ROAD2H. In: *MedRACER 2018*. October 29, 2018; Tempe, AZ.
69. Delaney BC, Curcin V, Andreasson A, *et al.* Translational medicine and patient safety in Europe: TRANSFoRm—Architecture for the learning health system in Europe. *Biomed Res Int* 2015; 2015: 961526.
70. Cook DA, Sorensen KJ, Linderbaum JA, *et al.* Information needs of generalists and specialists using online best-practice algorithms to answer clinical questions. *J Am Med Inform Assoc* 2017; 24 (4): 754–61.
71. Henry C, Etain B, Mathieu F, *et al.* A French network of bipolar expert centres: a model to close the gap between evidence-based medicine and routine practice. *J Affect Disord* 2011; 131 (1–3): 358–63.
72. Moja L, Kwag KH, Lytras T, *et al.* Effectiveness of computerized decision support systems linked to electronic health records: a systematic review and meta-analysis. *Am J Public Health* 2014; 104 (12): e12–22.
73. Kilsdonk E, Peute LW, Jaspers MWM. Factors influencing implementation success of guideline-based clinical decision support systems: a systematic review and gaps analysis. *Int J Med Inform* 2017; 98: 56–64.
74. Shahmoradi L, Safadari R, Jimma W. Knowledge management implementation and the tools utilized in healthcare for evidence-based decision making: a systematic review. *Ethiop J Health Sci* 2017; 27 (5): 541–58.
75. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003; 290 (12): 1624–32. doi : 10.1001/jama.290.12.1624.
76. Akyürek ÇE, Sawalha R, Ide S. Factors affecting the decision making process in healthcare institutions. *Acad Strategic Manag J* 2015; 14: 56.
77. Osop HB. A Practice-Based Evidence Approach for Clinical Decision Support [thesis]. Brisbane, Australia, Queensland University of Technology; 2018. doi : 10.5204/thesis.eprints.123320.
78. Plaisant C, Milash B, Rose A, *et al.* LifeLines: visualizing personal histories. In: proceedings of the SIGCHI Conference on Human Factors in Computing Systems; 1996: 221–7; Vancouver, British Columbia, Canada.
79. Shahar Y, Cheng C. Intelligent visualization and exploration of time-oriented clinical data. In: proceedings of the 32nd Annual Hawaii International Conference on Systems Sciences; 1999: 15–31; Maui, Hawaii.
80. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002; 359 (9302): 248–52.
81. LePendu P, Iyer SV, Fairon C, *et al.* Annotation analysis for testing drug safety signals using unstructured clinical notes. *J Biomed Semantics* 2012; 3 (Suppl 1): S5. doi : 10.1186/2041-1480-3-S1-S5
82. Jung K, LePendu P, Iyer S, et al. Functional evaluation of out-of-the-box text-mining tools for data-mining tasks. *J Am Med Inform Assoc* 2015; 22 (1): 121–31. doi : 10.1136/amiajnl-2014.
83. Overhage JM, Ryan PB, Reich CG, *et al.* Validation of a common data model for active safety surveillance research. *J Am Med Inform Assoc* 2012; 19 (1): 54–60.
84. Pathak J, Kho AN, Denny JC. Electronic health records-driven phenotyping: challenges, recent advances, and perspectives. *J Am Med Inform Assoc* 2013; 20 (e2): e206–11.