2021-11-07

Towards a framework for comparing functionalities of multimorbidity clinical decision support: A literature-based feature set and benchmark cases.

Dympna O'Sullivan
Technological University Dublin, dympna.osullivan@tudublin.ie

William Van Woensel
Dalhousie University

Szymon Wilk
Poznan University of Technology

Towards a framework for comparing functionalities of multimorbidity clinical decision support: A literature-based feature set and benchmark cases

Dympna O'Sullivan, PhD[1], William Van Woensel, PhD[2], Szymon Wilk, PhD[3], Samson W. Tu, MS[4], Wojtek Michalowski, PhD[5], Samina Abidi, MD PhD[6], Marc Carrier, MD[7], Ruth Edry, MD[8,9], Irit Hochberg, MD[8,9], Stephen Kingwell, MD[7,] Alexandra Kogan[10], MSc, Martin Michalowski, PhD[11], Hugh O'Sullivan, MD[12], Mor Peleg, PhD[10]

[1]ASCNet Research Group, Technological University Dublin, Dublin, Ireland
[2]NICHE Research Group, Dalhousie University, Halifax, Canada
[3]Institute of Computing Science, Poznan University of Technology, Poznan, Poland
[4]Center for BioMedical Informatics Research, Stanford University, Stanford, CA, 94305, USA
[5]Telfer School of Management, University of Ottawa, Ottawa, ON, Canada
[6]Medical Informatics Faculty of Medicine, Dalhousie University, Canada
[7]The Ottawa Hospital, Ottawa, ON, Canada
[8]Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel
[9]Rambam Medical Center, Haifa, Israel
[10]Department of Information Systems, University of Haifa, Haifa, Israel, 3498838
[11]School of Nursing, University of Minnesota, Minneapolis, MN, USA
[12]BJD Family Practice, Ballyjamesduff, Cavan, Ireland

Abstract

*Multimorbidity, the coexistence of two or more health conditions, has become more prevalent as mortality rates in many countries have declined and their populations have aged. Multimorbidity presents significant difficulties for Clinical Decision Support Systems (CDSS), particularly in cases where recommendations from relevant clinical guidelines offer conflicting advice. A number of research groups are developing computer-interpretable guideline (CIG) modeling formalisms that integrate recommendations from multiple Clinical Practice Guidelines (CPGs) for knowledge-based multimorbidity decision support. In this paper we describe work towards the development of a framework for comparing the different approaches to **m**ultimorbidity CI**G**-based **c**linical **d**ecision **s**upport (MGCDS). We present (1) a set of features for MGCDS, which were derived using a literature review and evaluated by physicians using a survey, and (2) a set of benchmarking case studies, which illustrate the clinical application of these features. This work represents the first necessary step in a broader research program aimed at the development of a benchmark framework that allows for standardized and comparable MGCDS evaluations, which will facilitate the assessment of functionalities of MGCDS, as well as highlight important gaps in the state-of-the-art. We also outline our future work on developing the framework, specifically, (3) a standard for reporting MGCDS solutions for the benchmark case studies, and (4) criteria for evaluating these MGCDS solutions. We plan to conduct a large-scale comparison study of existing MGCDS based on the comparative framework.*

Introduction

Most recommendations from clinical practice guidelines (CPGs) focus on the management of single diseases. Such recommendations may be harmful or impractical for patients with multimorbidity. Multimorbidity has been defined as one of the "grand challenges in clinical decision support" by Sittig et al[1] because of a difficulty with creating mechanisms to identify and eliminate redundant, contraindicated, potentially discordant, or mutually exclusive guideline-based recommendations. Using a computer language such as PROforma or GLIF3, one can computerize CPG as Computer-interpretable guidelines (CIGs)[2,3] that enable CIG-driven clinical decision support systems (CDSS). These have typically addressed a single morbidity as per the single-disease focus of the CPG they are ultimately based on. However, the rise in multimorbidity is driving the need for complex treatment plans with many potential interactions and adverse events among CIGs. Several researchers have begun developing **m**ultimorbidity CI**G**-based

clinical **d**ecision **s**upport (MGCDS) that can detect and mitigate interactions among recommendations belonging to different CIGs in order to develop non-conflicting management plans for patients with multimorbidity[4-10].

Given the number of active research groups and different MGCDS approaches, we decided to create a standard framework for comparing these approaches. Our framework consists of (1) the relevant features of the multimorbidity problem that should be addressed, (2) a set of benchmarking case studies that are representative and cover the features, (3) a standard for reporting the MGCDS solutions for the benchmarks, and (4) criteria for evaluating these solutions. We intend for this framework to be used in standardized evaluations of prior or new/updated MGCDS, to help assess their functionalities, and identify gaps in the state-of-the-art. This paper reports results of research on the first two parts of the framework. We will use the complete benchmark framework in a comparative MGCDS study, which is currently underway and involves a number of groups who have previously developed MGCDS. A companion paper, to be published after the comparative study has completed, will report on the development of part 3 and part 4 of the framework as well as the comparative study results themselves.

Background and related work

MGCDS has gained attention in recent years and multiple approaches have been proposed and described in the literature. A comprehensive review and comparison of relevant approaches are provided elsewhere[2,11,12], and here we summarize the relevant characteristics (e.g., an employed CIG representation formalism or reasoning method) of most recent proposals. We also point at clinical case studies that were used to test these approaches. We applied a semi-formal process to search for relevant publications. Specifically, we identified candidate papers based on the description of related works in two recent publications on MGCDS by Kogan et al.[6] and Michalowski at al.[7]. Then we limited the list of candidates to journal papers published in the last 5 years. Finally, we screened the eligible papers to select those that present the latest versions of MGCDS methodologies and illustrate their applications in case studies.

Kogan et al.[6] propose a goal-oriented MGCDS which frames patient management as a goal attainment problem. The methodology, implemented in the form of the GoCom system, relies on CIGs represented in PROforma and augmented with knowledge about goals and physiological effects of specific CIG tasks. This knowledge is encoded with standardized terms coming from controlled terminologies (e.g., SNOMED CT) and medical ontologies (e.g., NDF-RT). The planning algorithm used by GoCom operates on goal forests that capture goals associated with specific CIGs applied to the patient, identifies inconsistencies among goals and mitigates them by proposing alternative solutions. GoCom is able to reason at different abstraction levels (e.g., specific drugs and their classes) by exploring external ontologies and to generate explanations for specific solutions. Alternative solutions, together with supporting explanations, are then presented to the clinician who makes the final decision. GoCom relies on the HL7 FHIR standard to represent clinical data, thus facilitating integration with existing hospital information systems (HISs). GoCom was tested on 6 clinical scenarios involving concurrent application of multiple (2-3) CIGs -- one of the scenarios describing a patient being managed for stroke and duodenal ulcer (DU) and diagnosed with osteoporosis was used as the basis for development of Case 1 described in this paper. Moreover, GoCom was evaluated by medical students and interns in two empirical studies that confirmed its usefulness and validity of delivered recommendations.

Michalowski at al. describe MitPlan[7] – a planning-oriented MGCDS that frames multimorbid patient management as a planning problem that allows to mitigate adverse interactions between multiple CIGs and to derive safe management plans. MitPlan constructs a plan for a given time horizon that optimizes some objective function (e.g., overall cost) – with time horizon and objective function being specified by the clinician. It also considers patient preferences – if several options are possible, it selects the most preferred one. Unlike GoCom, MitPlan generates a single optimal management plan that is presented to the clinician for approval. It accepts CIGs represented as Actionable Graphs (AGs) that are based on the task-network model and can be easily derived from other representations, such as GLIF or PROforma. AGs are automatically transformed to Planning Domain Definition Language (PDDL) for further processing. PDDL is also used to represent secondary domain knowledge on possible interactions and strategies to mitigate them. MitPlan was evaluated by collaborating physicians using a scenario describing a patient suffering from chronic kidney disease (CKD) and hypertension (HT), who experiences an acute episode of atrial fibrillation (AF). This scenario was used as a basis for development of Case 2 described in this paper.

Jafarpour et al.[8] propose an ontology-based MGCDS for execution-time integration of multiple CIGs. The approach assumes integration points need to be first identified by the clinician, and then appropriate integration policies are instantiated and applied to mitigate adverse interactions at execution-time. Integration policies are defined using the CIG-IntO ontology that is represented in OWL and processed by a standard OWL reasoner (the authors employ Jena). The approach is able to discover drug-drug and drug-disease interactions using the Bio2RDF DrugBank ontology, handle temporal aspects of mitigation (e.g., delaying tasks to avoid conflicts), and rollback integration policies that

are no longer safe or efficient at execution-time. CIG-IntO also allows for defining conditional integration policies where revisions introduced to CIGs may be further customized depending on additional conditions, e.g., related to the patient's health profile. This increases the flexibility and generality of integration policies. Moreover, in addition to mitigation integration policies the authors also propose optimization integration policies that minimize resource use and costs by removing redundant tasks from management plans and re-using test results. The approach was tested using 6 case studies with pairs of CIGs and positively evaluated by a panel of health informaticians and physicians.

Another MGCDS is presented by Fdez-Olivares et al.[9] who propose a Multi-Agent Planning (MAP) framework. The MAP framework relies on Hierarchical Task Networks (HTNs) to represent and control the planning process and involves multiple agents that develop different candidate management plans. Possible plans are evaluated using an objective function that considers plan cost and complexity assessed according to the patient's quantitative preferences. Finally, the optimal plan is presented to the clinician for approval. MAP accepts CIGs represented in Hierarchical Planning Description Domain Language (HPDL) – such representation can be obtained from the CIGs modelled in Asbru formalism. Proposed approach uses HPDL to capture possible adverse interactions and patient's qualitative preferences related for example to the mode of drug administration or frequency of administration – these preferences are considered when constructing candidate plans. As with the approach by Jafarpour et al. [8], MAP takes into account temporal aspects of interactions and mitigation. MAP was evaluated using a case study involving a patient with diabetes mellitus (DM) and hypertension (HT) and managed at different time points of disease progression and treatment process.

Piovesan et al.[10] describe the MGCDS implemented as the GLARE-SSCPM system. The proposed system relies on multiple methods to identify interactions and mitigate them, such as temporal reasoning, cost-benefit analysis and model-based verification. The system employs ontology with medical CIG-independent knowledge represented in OWL (so it can be processed with standard reasoners), developed in collaboration with domain experts and integrating parts of SNOMED CT and ACT terminologies. GLARE-SSCPM accepts CIGs represented in the GLARE formalism as conditional and hierarchical graphs. Similarly to GoCom, the authors adopt the mixed initiative planning paradigm where the final management plan is developed by the clinician who interacts with the system following the "focus, hypothesize and test" modality. Specifically, the system supports the clinician in focusing on relevant parts of CIGs (where adverse interactions may occur), identifying alternative management options and testing these options in "what-if" analysis. GLARE-SSCPM was tested on a case study of a patient suffering from venous thrombosis (VT) and peptic ulcer (PE).

Zamborlini et al.[4] propose MGCDS that combines the Transition-based Medical Recommendation (TMR) knowledge representation model with first-order logic (FOL) rules. The TMR model describes CIG recommendations augmented with additional domain knowledge, such as causes and effects of actions and possible interactions between recommendations. Similarly to GoCom, recommendations are associated with goals and these recommendations may have negative, neutral or positive contributions towards the goals. FOL rules are used to identify interactions between multiple CIGs based on the knowledge encapsulated by corresponding TMR models. These models are generic and reusable, thus they do not need to be customized to specific CIGs and in this sense they are similar to integration policies introduced in CIG-IntO. The proposed approach was tested in complex case study of a patient with breast cancer and three additional multimorbidity conditions: osteoarthritis (OA), HT and congestive heart failure (CHF).

As shown in the above summary, there are multiple approaches to creating MGCDS. These approaches have diversified (but often complementary) capabilities, use different representations of the CIGs and related domain knowledge, and use different methods to develop management plans. Moreover, they were assessed using unique case studies, which makes their comparison from methodological and practical perspectives even more challenging. We believe a comprehensive comparative framework, similar to the one developed to compare CIG representations[12], should facilitate MGCDS comparison of functionalities, provide a common platform for presentation of various approaches, and support development of new ones.

Methods

Our methodology for identifying and confirming the features of the MGCDS consisted of three parts. First, we conducted a literature review to identify features of MGCDS used by research groups in the field. Second, we created a number of case studies that embody these features. Finally, we developed a survey whereby physicians were asked to confirm and comment on the list of identified MGCDS features.

Identification of MGCDS features

Most of the research on MGCDS is published in several health informatics journals, such as Journal of Biomedical Informatics, Journal of American Medical Informatics Association, International Journal of Medical Informatics, Methods of Information in Medicine, Journal of Medical Systems, and Artificial Intelligence in Medicine. In line with the PRISMA systematic review process[13], we searched Google Scholar, PubMed and Web of Science with relevant keywords, screened the title and abstracts of the records found, assessed eligibility of the full-text, and finally reviewed the remaining publications. As a result of this review we identified 18 multimorbidity features, spread across the reviewed publications, which can be categorized as follows: (a) interactions among recommendations coming from disease-specific CIGs; (b) mitigation strategies when CIGs offer interacting recommendations; and (c) other possible features. Features from category (a) were identified based on clinical case studies presented in the literature, whereas features from categories (b) and (c) were identified based on the approaches to integrating comorbid CIGs. A complete list of features together with illustrative examples is presented in Table 1.

Case studies to demonstrate MGCDS features

All groups with prior work on MGCDS were invited to contribute relevant case studies, i.e., cases where recommendations from different clinical guidelines result in adverse interactions or introduce resource inefficiencies for a multimorbidity patient. These case studies were either based on previously published examples for demonstrating their multimorbidity decision-support methods, or represented new case studies that similarly illustrated the identification and/or mitigation of adverse interactions.

Initially, the groups were provided with a sample multimorbidity case study from Kogan et al.[6] in a uniform, comprehensive format, supplemented by references to specific statements from the CPGs involved, the set of interactions to be detected and the solution – i.e., sets of treatment options that mitigate the multimorbidity interactions. We asked the groups to submit case studies in this uniform format. We selected a minimal set of submitted case studies (4) that together cover the full set of the previously identified multimorbidity features. The 4 case studies provide good coverage of the features - 9 of the 18 features are demonstrated in 2 -3 case studies. The case studies were reviewed by clinical partners for correctness. The 4 case studies are intended as a starting point to begin the comparison study of existing MGCDS; additional case studies will be added as the research progresses.

Next, we revised and expanded the selected case studies based on a rigorous process, which started with a review of the CPG repositories to identify updated versions of the guidelines and supplementary references for specific statements and actions. Collaborating medical experts were consulted for validating the clinical accuracy of the cases. As a result, we were able to establish a set of validated interactions together with the set of treatment options to be considered. Representative synthetic patient scenarios were developed with the help of medical experts and added to each of the case studies.

Validation of the MGCDS features

We started by consulting members of the groups with prior work on MGCDS to review and comment on the set of 18 MGCDS features. Secondly, we developed an online survey using the Qualtrics platform to survey physicians in order to determine the validity of the proposed MGCDS features for our framework. Physicians were recruited to complete the survey via convenience sampling. The survey preamble introduced physicians to the purpose of the study and defined notions of adverse interactions and mitigation strategies in the context of the MGCDS. The survey included 18 questions partitioned into three sections - the first section was devoted to the adverse interactions that may occur as a result of applying guidelines (7 identified features), the second section was devoted to types of mitigations to be applied when addressing such interactions (7 identified features), and the third section was devoted to other possible features of MGCDS (4 identified features). Short examples from the developed case studies were included to illustrate each feature. Physicians were asked to evaluate whether each identified feature was relevant or not for the multimorbidity problem. At the end of each section, they were provided an opportunity to add and describe any missed features. The survey was piloted with two physicians and adjustments to the phrasing of the questions was made based on their feedback. The final version of the survey can be viewed at our GitHub repository[14].

Results

Case study descriptions

Twelve case studies were contributed by four of the participating groups. The minimal set of cases, which cover all identified features of MGCDS, included four cases provided by three groups and are summarized below. The full case descriptions can be accessed at our GitHub repository[14].

Case 1, adapted from Kogan et al.[6], involves three cascading morbidities. The first morbidity was managed with a drug, resulting in an adverse drug event (ADE). The ADE is regarded as another morbidity and is treated with a drug, resulting in a second ADE, which is regarded as a third morbidity. The possible mitigation strategies include either (a) adding a drug for the third morbidity; or (b) preventing one of the ADEs by replacing or stopping the drug that caused it. The various management plans may meet all clinical goals (address all current morbidities) or may compromise one of them. Specifically, Case 1 describes a patient that is on aspirin for prevention of stroke, which causes DU due to NSAID, which has been treated by stopping aspirin and adding omeprazole (a proton pump inhibitor, PPI). Aspirin was continued with the PPI to prevent DU recurrence. Now secondary osteoporosis is diagnosed, caused by the PPI.

Case 2, adapted from Michalowski et al.[7] involves three morbidities that need to be simultaneously managed, while at the same time considering patient preferences. It describes a situation where a patient successfully treated for two concurrent conditions is diagnosed with a third one and this new diagnosis triggers the need for a revised treatment plan. The mitigation strategies include (a) making more aggressive treatment of one of the underlying conditions, and (b) managing drug contraindications and interactions. Additionally, when developing a management plan, the patient's preferences need to be taken into account. Specifically, Case 2 describes a patient suffering from CKD and HT that are managed with ACE inhibitors, calcium channel blockers (CCB), diuretics, and low dosage aspirin (for prevention of cardiovascular disease). New diagnosis of atrial fibrillation requires the following, in line with the strategies described above: (a) replacing aspirin with an anticoagulant (warfarin) for more aggressive anticoagulant treatment, and (b) using sodium channel blockers (SCB) instead of potassium channel blockers (PCB) in anti-arrhythmic therapy (as PCB is contraindicated for the CKD patients), and abandoning beta blocker medication routinely used for rate control because of its possible interactions with ACE inhibitors or CCB. In light of patient preferences, warfarin is replaced with one of the direct anticoagulants.

Case 3, adapted from Jafarpour et al[8], involves two morbidities where clinical guidelines recommend adversely interacting drug treatments, both of which are nevertheless needed for treating the multimorbid conditions. The mitigation strategies include (a) increased frequency in monitoring relevant vital signs during concomitant drug treatment; and (b) adjusting drug dosage to compensate for negative evolutions of these vital signs. Further, increased frequency of monitoring must be maintained after completing one of the drug treatments until stable vital signs are observed. Specifically, Case 3 describes a patient with venous thromboembolism (VTE) and bacterial urinary tract infection (UTI) where VTE is managed by warfarin and UTI is managed by antibiotic such as trimethoprim–sulfamethoxazole (TMP/SMX). Warfarin was chosen due to availability of specific reversal agents (e.g., vitamin K); and TMP/SMX because of its low cost, effectiveness and familiarity among clinicians. During concomitant treatment, it is recommended to increase the monitoring frequency of the patient's international normalized ratio (INR) value (e.g., daily) and adjust warfarin dosage accordingly. Upon completion of the antibiotics regimen, the increased measuring frequency should be kept in place until a stable INR is observed. At that point, regular INR monitoring should commence.

Case 4, developed especially for this study by coauthors AK, RE, MP and SWT, involves temporally managing a multimorbidity patient who needs to undergo an emergent surgical procedure. Because of the procedure, the patient has a new health risk that cannot be simultaneously addressed with other multimorbidity risks. The mitigation strategies include (a) focusing on surgery for the urgent condition; (b) suspending a long acting irreversible antagonist drug that adversely interacts with the treatment from *(a)*; and (c) replacing it with a short acting reversible antagonist drug to minimize the time that the patient is unprotected by suspending *(b)*. Specifically, Case 4 describes a cardiac patient with high cardiovascular risk that is on dual antiplatelet (aspirin and clopidogrel, a P2Y12 inhibitor) for 12 months following implantation of drug-eluting stent for prevention of stroke. Two months after stent implantation he is diagnosed with lung mass and needs to undergo an urgent surgical procedure that cannot be postponed past 12 months after the stent implantation—this places him at high risk for surgical bleeding due to concomitant dual antiplatelet treatment. To manage the risk, the long acting irreversible antagonist drug (clopidogrel) is suspended five days before surgery until 12-24 hours after surgery. Bridging therapy with the short acting reversible antagonist (tirofiban) is recommended. Tirofiban is started 48 hours after clopidogrel is suspended, continued until 4 hours before surgery to allow time for the drug to dissociate from platelet receptors and allow for normal aggregation and coagulation during surgery. After surgery either clopidogrel or tirofiban are resumed as soon as possible, depending on the expected degree of post operative bleeding.

Features of MGCDS

Table 1 lists and provides examples for the 18 MGCDS features. The table also points to the case studies that cover the features.

Table 1. Identified MGCDS features

Feature	Short example	Captured by case study
Interaction features		
A1. Drug from a CPG has an effect on a comorbid condition.	The cardiovascular disease CPG recommends low-dose aspirin, which may cause or worsen duodenal ulcer (DU) as a comorbid condition.	1,2,4
A2. Two or more drugs from different CPGs interact	The bacterial urinary tract infection CPG recommends antibiotics such as trimethoprim, which impacts the anticoagulant effect of warfarin that is recommended by the venous thromboembolism CPG.	2,3
A3. Clinical goals from different CPGs conflict	Coronary artery disease CPG recommend preventing thrombosis via anti-platelet therapy, which conflicts with the goal of preventing bleeding during surgery, as per perioperative antiplatelet therapy CPG.	4
A4. Conflicting actions (e.g., drugs, procedures) from different CPGs	The transient ischemic attack (TIA) CPG recommends administration of clopidogrel, while coronary artery bypass grafting CPG recommends suspending clopidogrel.	1
A5. Duplicate or redundant advice from different CPGs	Hypertension and cardiovascular disease CPGs both recommend calcium channel blockers.	4
A6. Temporal relationship between different CPGs	The acute otitis media CPG recommends taking cefpodoxime two hours after taking antacids, which are in turn recommended by the gastroesophageal reflux disease CPG.	4
A7. Multiple related interactions from different CPGs	The TIA CPG recommends aspirin, whereby the DU CPG recommends proton pump inhibitors (PPI) to mitigate the effect of aspirin on the duodenum or ulcer bleeding. PPI may cause a new comorbid condition of osteoporosis.	1,4
Mitigation features		
A8. Adding a drug to mitigate an adverse effect	Add a PPI to mitigate the effect on DU caused by aspirin.	1
A9. Adjust drug dosage	A reduction of 10% of warfarin dosage to cope with concomitant treatment of antibiotics.	3,4
A10. Monitor the effect of a drug	Monitor progression of the DU during overlapping treatment with aspirin; or monitor INR frequently during concomitant treatment of warfarin and antibiotics.	3
A11. Replacing a drug with a safer / more effective drug for comorbidity	Replace aspirin with clopidogrel for a patient with DU.	1,2,4
A12. Discard unsafe/interacting drug	Suspend ACE Inhibitor when eGFR value drops by over 30% over 4 months.	1,2,4
A13. Delay a task to avoid a temporal overlap	Stop clopidogrel 5 days prior to surgery to reduce bleeding risk.	4
A14. Add a task to ensure a temporal overlap	When stopping clopidogrel prior to surgery, start bridging therapy with tirofiban 24h later until 4h before surgery, and resume 2h after surgery.	4
Other features		
A15. Patient preferences and/or patient burden	Choosing one drug over another due to lower price; or choosing any of direct oral anticoagulants over warfarin to avoid checking INR on regular basis.	1,2,3,4

A16. Optimization of clinical resources	Grouping tests recommended by different CPG on the same day, or avoiding multiple imaging scans, recommended by different CPG, where results can be re-used for diagnosis of both comorbid illnesses.	2
A17. Explanation of the mitigation strategy(ies)	Including an explanation for a recommended mitigation (e.g., all patient conditions are treated, the largest number of conditions are treated, or the condition that is at the focus of the medical investigation is treated).	1,4
A18. Alternative mitigation strategies for a single interaction	For a patient taking aspirin for secondary prevention of TIA, who developed DU due to aspirin, one strategy may be to add a PPI to protect the duodenum, and a second strategy may be to replace aspirin with clopidogrel.	1,4

Validation of MGCDS features

Members of all groups with prior work on MGCDS were asked to review the identified MGCDS features and to suggest any missing ones. The 11 group members who responded were positive about the set of 18 proposed features and did not suggest any new ones. After this initial validation, we developed and validated an online survey and recruited 15 physicians of different specialties and different levels of experience for assessing and commenting on the features. The survey was completed by all invited physicians. The results are presented in Table 2.

Overall, the results of the survey confirmed the relevance of the identified MGCDS features. There were only a few instances where physicians did not endorse the features unanimously and these are outlined here. Regarding features associated with interactions among recommendations coming from disease-specific CPGs, identification of *duplicate or redundant advice from different CPGs (A5)* was found to be relevant by 9 out of 15 physicians while identifying *temporal relationship between different CPGs (A6)* and identifying *conflicting actions from different CPGs (A4)* were found to be relevant by 13 and 14 out of 15 physicians, respectively. Regarding features associated with the mitigation strategies when CPGs offer interacting recommendations, the mitigation strategies of *monitoring the effect of a drug (A10)* and *replacing a drug with a safer/non-interacting drug/more effective drug for comorbidity (A11)* were found to be relevant by 13 and 14 out of 15 physicians, respectively. The least agreement among the physicians was observed for the other possible features' category. Here, only identification of *alternative mitigation strategies for a single interaction* received unanimous support. Fewer physicians were convinced that *explanation of the mitigation strategy(ies) (A17)* with 11 positive responses out of 15, *optimization of clinical resources (A16)* with 12 positive responses out of 15, and inclusion of *patient preferences and/or patient burden (A15)* with 14 positive responses out of 15 are relevant.

Table 2. Physician responses to survey

Features of the multimorbidity CPG problem	#Physicians who found the features relevant (out of 15)
Interactions among CPGs' advice	
A1. Drug from a CPG has an effect on a comorbid condition	15
A2. Two or more drugs from different CPGs may interact	15
A3. Clinical goals from different CPGs may conflict	15
A4. Conflicting actions (e.g., drugs, procedures) from different CPGs	14
A5. Duplicate or redundant advice from different CPGs	9
A6. Temporal relationship between different CPGs	13
A7. Multiple related interactions from different CPGs	15
Mitigation strategies when CPGs offer interacting advice	
A8. Adding a drug to mitigate an adverse effect	15

A9. Adjust drug dosage	15
A10. Monitor the effect of a drug	13
A11. Replacing a drug with a safer / non-interacting drug / more effective drug for comorbidity	14
A12. Discard unsafe/interacting drug	15
A13. Delay a task to avoid a temporal overlap	15
A14. Add a task to ensure a temporal overlap	15
Other possible features	
A15. Patient preferences and/or patient burden	14
A16. Optimization of clinical resources	12
A17. Explanation of the mitigation strategy(ies)	11
A18. Alternative mitigation strategies for a single interaction	15

Physicians did not indicate that any features were missing from the set provided for evaluation. Physicians made few comments mostly related to prioritizing goals from CPGs: one suggestion was to ignore actions that are associated with less important goals and prioritizing goals based on clinical needs. Another physician suggested that goals should be prioritized based on what treatment a patient can or is willing to follow. Finally, one physician commented that the most difficult aspect of MGCDS is an assessment of risks and benefits when guidelines are in conflict.

Discussion and Future Work

Multimorbidity is complex clinically but also challenging for effective decision support. This challenge is manifested by a relatively large number of published MGCDS, with none of them covering all possible features associated with supporting the management of multimorbidity patients. Therefore, it is important that there is a unified framework that, on the one hand, allows for comparing functionalities of existing MGCDS, and, on the other hand, can help guide development of new ones by highlighting gaps in the state-of-the-art. The purpose of the research described in the paper was to create such a framework. We have identified a set of MGCDS features, developed 4 case studies to cover those features and conducted a survey with physicians to confirm the features.

The survey results largely confirmed the feature set. There were three features where relevance was somehow questionable for the physicians. Five respondents did not consider *duplicate or redundant advice of different CPGs (A5)* as a relevant feature. The most plausible explanation is that experienced clinicians find such advice to be rather straightforward. However, considering that an MGCDS might be used by physicians of different levels of experience, having such a feature may be useful. Similarly, three physicians considered *explanation of mitigation strategy(ies) (A17)* to be less relevant. Such thinking seems to be related to the ongoing discussion in the medical informatics community about the "black box algorithm effect", with some arguing for system explainability while others focus on the quality of performance of a black box algorithm. It is our assertion that the assessment of this feature reflects this debate. Finally, two physicians asserted that *optimization of clinical resources (A16*) is not relevant. In our context, optimization of the resources implies avoiding unnecessary tests or grouping these tests together so they can be conducted during one visit. While this is probably one of the most relevant features from a patients' perspective, physicians consider such optimization to be beyond scope of their practice and being under control of laboratory and imaging services.

The strengths of our method to develop this comparative framework includes the thorough review and analysis of the existing MGCDS literature, the participation of original developers of various guideline-based multimorbidity methods, the rigorous vetting of the cases by physicians, the confirmatory survey by physicians not involved in the development process, and the upcoming comparison study that will use, refine, and extend the framework. At the same time, we recognise certain limitations. Firstly, our sample size of physicians is small (15 physicians), however, we believe it achieves the goal of verifying the validity of features at this point in the work, and we intend to validate the MGCDS framework with a larger group of physicians in the upcoming phases of our work. Second, given that we

derived the set of interaction, mitigation, and other features from a review of the existing MGCDS literature, it is possible that additional features may be discovered as researchers work on new domains and new combinations of morbidities. Thus, this framework will necessarily be an evolving one and will merit future reviews. Finally, another limitation of our method is that we did not mine the clinical literature for potential sources of new features. While many of us were inspired by the landmark 2005 Boyd et al. paper[15], it is beyond our expertise and scope to review the clinical literature for interesting and novel multimorbid interactions and mitigations. Nevertheless, given the rigorous review of the case studies and the affirmation of the features by physicians—whereby no additional features were suggested, with one caveat (see below)—we are confident about the robustness of the case studies and the multimorbidity features that we have identified. It is our hope that this comparative framework and upcoming study will be of interest not only to informaticians, but to clinicians as well. With a consolidation of existing understanding of multimorbidity interactions and mitigations, we will be in the position to have further dialog between informaticians and clinicians.

Another aspect of our framework is that it is more methodologically-oriented than implementation-oriented—meaning that it is focused on high-level features and mitigation strategies rather than concrete implementation and deployment methods. What the groups contributing to this framework share is that they have developed MGCDSs that in totality cover the identified features. Originally some of us hoped that the framework and the survey could shed new light on the requirements of implementing MGCDS as well. However, the implementation of MGCDS as actual systems for deployment depends on myriad factors (e.g., the target audience and the workflow settings) beyond what the framework can accommodate. The downgrading of explainability and optimization of clinical resources by some physicians may also be a reflection of this issue.

The clinicians' comments about the need to prioritize conflicting goals or weighing risks and benefits of different actions suggest that a new "other feature" may possibly be relevant, which focuses on explicit support for decision making among conflicting goals and actions. Some approaches in the literature already provide such decision support. For example, MitPlan[7] tries to optimize an objective function (e.g., overall cost) that is selected by the clinician. GoCom[6] makes the choices among different alternatives explicit, some of which may not satisfy a given guideline-suggested goal, but does not support weighing the priorities, costs and benefits, and trade-offs among the alternatives.

We plan to complete (3) a reporting standard for MGCDS solutions and (4) criteria for evaluating MGCDS solutions of our framework as part of the upcoming comparison study. In this study, we will use the complete comparative framework to evaluate the existing MGCDSs with direct involvement from groups that designed the systems. A quantitative evaluation will assess functionalities of MGCDS and in a qualitative evaluation we will interview physicians about the MGCDS solutions. We will also use a larger set of case studies, including real world case studies, investigate further conflicts and how to mitigate these conflicts, and explore the identification of further possible MGCDS features with physicians. A companion paper describing comparison study will present the development of part 3 and part 4 of the framework as well as the study results themselves. A reporting template will necessarily incorporate some evaluation criteria of the MGCDS systems themselves (e.g., the use of standard terminologies or knowledge sources). Several groups are already piloting a reporting template proposal, using not only their own cases but also external cases as exemplars. We expect to present the piloted reporting templates and a few reporting exemplars to the groups participating in the comparison study and iteratively refine them to the groups' satisfaction. Once the comparison study starts, we expect each group to implement guideline fragments sufficient to execute the common cases to the extent possible and then to report on their results.

To summarize, the results described in this paper represent first steps towards creating a validated, comprehensive framework for comparing functionalities of MGCDS. Having such a framework should help with identifying gaps in MGCDS research and subsequently help with moving this research area forward. In order to facilitate this progress, we plan to prospectively evaluate our proposed framework by inviting different research groups working on MGCDS to use the framework and its accompanying clinical use cases. This should help with identifying gaps in MGCDS research as well as provide guidance for future research directions.

References

1. Sittig D, Wright A, Osheroff J, BMiddleton B, Teich J, Ash J, et al. Grand challenges in clinical decision support. J Biomed Inf. 2008;41(2):387–92.2.
2. Peleg M, Tu SW, Bury J, Ciccarese P, Fox J, Greenes RARA, et al. Comparing Computer-Interpretable Guideline Models: A Case-Study Approach. J Am Med Inf. Assoc. 2003;10(1):52–68.
3. Peleg M. Computer-interpretable clinical guidelines: A methodological review. J. Biomed. Inform. 2013;46(4):744–63.

4. Zamborlini V, da Silveira M, Pruski C, ten Teije A, Geleijn E, van der Leeden M, et al. Analyzing interactions on combining multiple clinical guidelines. Artif Intell Med. 2017;81:78–93.
5. López-Vallverdú JA, Riano D, Collado A. Rule-based combination of comorbid treatments for chronic diseases applied to hypertension, diabetes mellitus and heart failure. LNCS 7738; 2013: 30-41.
6. Kogan A, Peleg M, Tu SW, Allon R, Khaitov N, Hochberg I. Towards a goal-oriented methodology for clinical-guideline-based management recommendations for patients with multimorbidity: GoCom and its preliminary evaluation. J. Biomed. Inform. 2020;112:https://doi.org/10.1016/j.jbi.2020.103587.
7. Michalowski M, Wilk S, Michalowski W, Carrier M. MitPlan: A planning approach to mitigating concurrently applied clinical practice guidelines. Artif Intell Med. 2021 Feb 1;112:102002.
8. Jafarpour B, Raza S, Woensel W Van, Sibte S, Abidi R. Execution-time integration of clinical practice guidelines to provide decision support for comorbid conditions. Artif Intell Med [Internet]. 2019;94(November 2018):117–37. Available from: https://doi.org/10.1016/j.artmed.2019.02.003
9 Fdez-Olivares J, Onaindia E, Castillo L, Jordán J, Cózar J. Personalized conciliation of clinical guidelines for comorbid patients through multi-agent planning. Artif Intell Med [Internet]. 2019;96(November):167–86. Available from: https://doi.org/10.1016/j.artmed.2018.11.003
10. Piovesan L, Terenziani P, Molino G. GLARE-SSCPM: An Intelligent System to Support the Treatment of Comorbid Patients. IEEE Intell Syst. 2018;33(6):37–46.
11. Riaño D, Ortega W. Computer technologies to integrate medical treatments to manage multimorbidity. J Biomed Inform [Internet]. 2017;75(September):1–13. Available from: http://dx.doi.org/10.1016/j.jbi.2017.09.009
12. Bilici E, Despotou G, Arvanitis TN. The use of computer-interpretable clinical guidelines to manage care complexities of patients with multimorbid conditions: A review. Digit Heal. 2018;4:205520761880492.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
14. GitHub repository for MGCDS benchmark framework research. https://github.com/MGCDS/benchmark-framework.
15. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005 10;294(6):716-724.