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Towards a goal-oriented methodology for clinical-guideline-based management recommendations for patients with multimorbidity: GoCom and its preliminary evaluation

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ABSTRACT

Patients with chronic multimorbidity are becoming more common as life expectancy increases, making it necessary for physicians to develop complex management plans. We are looking at the patient management process as a goal-attainment problem. Hence, our aim is to develop a goal-oriented methodology for providing decision support for managing patients with multimorbidity continuously, as the patient's health state is progressing and new goals arise (e.g., treat ulcer, prevent osteoporosis). Our methodology allows us to detect and mitigate inconsistencies among guideline recommendations stemming from multiple clinical guidelines, while consulting medical ontologies and terminologies and relying on patient information standards. This methodology and its implementation as a decision-support system, called GoCom, starts with computer-interpretable clinical guidelines (CIGs) for single problems that are formalized using the PROforma CIG language. We previously published the architecture of the system as well as a CIG elicitation guide for enriching PROforma tasks with properties referring to vocabulary codes of goals and physiological effects of management plans.

In this paper, we provide a formalization of the conceptual model of GoCom that generates, for each morbidity of the patient, a patient-specific goal tree that results from the PROforma engine's enactment of the CIG with the patient's data. We also present the "Controller" algorithm that drives the GoCom system. Given a new problem that a patient develops, the Controller detects inconsistencies among goals pertaining to different comorbid problems and consults the CIGs to generate alternative non-conflicted and goal-oriented management plans that address the multiple goals simultaneously. In this stage of our research, the inconsistencies that can be detected are of two types – starting vs. stopping medications that belong to the same medication class hierarchy, and detecting opposing physiological effect goals that are specified in concurrent CIGs (e.g., decreased blood pressure vs. increased blood pressure). However, the design of GoCom is modular and generic and allows the future introduction of additional interaction detection and mitigation strategies. Moreover, GoCom generates explanations of the alternative non-conflicted management plans, based on recommendations stemming from the clinical guidelines and reasoning patterns.

GoCom's functionality was evaluated using three cases of multimorbidity interactions that were checked by our three clinicians. Usefulness was evaluated with two studies.

The first evaluation was a pilot study with ten 6th year medical students and the second evaluation was done with 27 6th medical students and interns. The participants solved complex realistic cases of multimorbidity patients: with and without decision-support, two cases in the first evaluation and 6 cases in the second evaluation.

Use of GoCom increased completeness of the patient management plans produced by the medical students from 0.44 to 0.71 (P-value of 0.0005) in the first evaluation, and from 0.31 to 0.78 (P-value < 0.0001) in the second evaluation. Correctness in the first evaluation was very high with (0.98) or without the system (0.91), with non-significant difference (P-value ≥ 0.17). In the second evaluation, use of GoCom increased correctness

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from 0.68 to 0.83 (P-value of 0.001). In addition, GoCom's explanation and visualization were perceived as useful by the vast majority of participants.

While GoCom's detection of goal interactions is currently limited to detection of starting vs. stopping the same medication or medication subclasses and detecting conflicting physiological effects of concurrent medications, the evaluation demonstrated potential of the system for improving clinical decision-making for multimorbidity patients.

1. Introduction

Patients with chronic multimorbidity are becoming more common as life expectancy of the population increases, making it necessary for physicians to develop complex management plans that address the many potential interactions among the patient's morbidities, medications, and adverse events [1]. To do so, physicians may consult evidence-based clinical practice guidelines (CPGs) and computer interpretable guidelines (CIGs) that support their decision-making. However, both CPGs and CIGs typically focus on a single medical condition and physicians are not supported with resolving the interactions that occur in multimorbidity. The Institute of Medicine notes that patients with comorbidity should be discussed in clinical practice guidelines, while explicitly specifying treatment goals as part of clinical guidelines and validating that treatment plans meet these goals; goals present an especially important consideration when considering multimorbidity patients, along with the priority of meeting each goal in the case of conflict, the quality of evidence for patient with comorbidities, the prevalence of interactions, the complexity of the regimen, and the burden of therapy [2,p. 127].

Clinical decision-making and therapy planning are based on defining clinical goals and proposing plans that meet them. Earlier studies proposed that modeling CIGs using goals has advantages for critiquing care plans [3], for proposing alternative plans when exceptions are detected [4], or for supporting explanations and easing CIG evolution [5].

We are looking at the patient management process as a goal-attainment problem. Hence, the focus of our research is to develop and evaluate a goal-oriented algorithmic methodology for integrating the knowledge of CIGs for different chronic diseases with general medical knowledge to help manage multimorbidity patients continuously, as their health state is progressing. The approach allows us to detect unmet goals and conflicting guideline recommendations that may result in adverse effects or less effective management plans. Moreover, the approach allows us to propose and explain non-conflicting management plans for patients with chronic multimorbidity that meet the goals associated with the different morbidities. **Unlike existing methods, the methodology leverages existing health standards and specifies CIGs as goal-oriented modular management plans**.

Drawing on information provided in clinical practice guidelines we specify a plan in terms of clinical goals (i.e., process-oriented goals such as diagnosing problem, managing (treat or prevent) a patient's problem, prescribing a medication or state-achievement goals that achieve a physiological effect (e.g., decreased blood pressure). This allows the detection of goals that are not met, conflicting goals, and finding alternative actions that concurrently meet these goals without conflict, based on the CIGs and potentially also on general medical knowledge bases. This makes the approach flexible (rather than having rigid action flowcharts), enables reuse, and supports reasoning at different levels of abstraction – from high-level diagnostic or management (i.e., treatment or prevention) goals, to physiological effects of medications, to specific management plans. Because **go**al modeling is key to the ability of our approach to support reasoning over **com**orbidities, we call our approach GoCom.

In an earlier paper we presented the Model-View-Controller software architecture [6] of the GoCom decision-support system [7], shown in Fig. 1. We use the PROforma formalism [8] as our standard for CIG representation. The integration of knowledge and data is facilitated by our novel use of annotating PROforma tasks with notation that refers to standard patient information classes (HL7 Fast Healthcare Interoperability Resources (FHIR) [9]), to goals formulated in terms of the vocabulary provided by medical ontologies (e.g., U.S. Department of Veteran Affairs (VA)'s National Drug File Reference Terminology (NDF-RT)[10]), and to medical terms taken from controlled terminologies (e.g., SNOMED-CT and MedDRA).

In this paper, we formalize, for the first time, the conceptual model of GoCom that supports the definition of a patient-specific goal tree for each CIG and that reasons to detect and mitigate conflicts among goals in the goal forest.

Relative to Kogan et al. [7], this paper describes extensions of GoCom's Controller algorithm that implement the planning model and provides: (a) support for ***reasoning along different levels of abstraction*** using NDF-RT's classification hierarchies (e.g., Aspirin is-a NSAID); (b) new ***aggregation patterns*** that allow combining recommendations from multiple guidelines into sets of clinical actions for the goals arising from multiple CIGs. This is in contrast to the approach we published before, in which the clinicians using of the system received the recommendations one by one; and (c) ***explanation-generation*** capability that, together with the aggregation pattern, allows clinicians who use GoCom's decision support to view the management plan while considering all multimorbidity goals. We further present results of an evaluation study with ten sixth-year medical students that demonstrated that GoCom's decision-support for multimorbidity patients increased the completeness of diagnosis and management actions relative to the gold standard, as compared with students from the same group who received no decision support. Correctness was very high with or without GoCom.

2. Related work

We refer the readers to Kogan et al. [7] for a summary of the PROforma [8] formalism and HL7′s FHIR [9] patient data model. Below we discuss the state of the art in CIG formalisms and approaches for integrating CIGs for multimorbidity patients.

2.1. Computer-interpretable guidelines (CIG) representation formalisms

Most of the CIG formalisms are task-network models (TNM) that hierarchically decompose clinical guideline algorithms (i.e., care processes) into networks of tasks that unfold over time. A variety of task-network CIG languages have been developed over the years [11,12], including Asbru, EON, GASTON, GLARE, GLIF3, Guide, HELEN, PROforma, and SAGE. The review [11] compares the most prominent features of these formalisms. Below we detail features that are common to all TNMs and elaborate more on PROforma, which is the CIG formalism selected for this research.

All of the TNM formalisms have editing tools that support the visualization of clinical algorithms for easing human comprehension as well as for computable specification and for allowing automatic interpretation and enactment by enactment engines. As was originally conceived in its deliberately simple task model [13], PROforma supports networks whose nodes are tasks belonging to four types: action, decision, data enquiry, or hierarchical plans. Tasks may be performed in sequence or in parallel. Decision-making logic that is supported by all TNM formalisms allows the representation of if-then-else rules. PROforma was the first formalism to support also argumentation logic, where rules in favor of

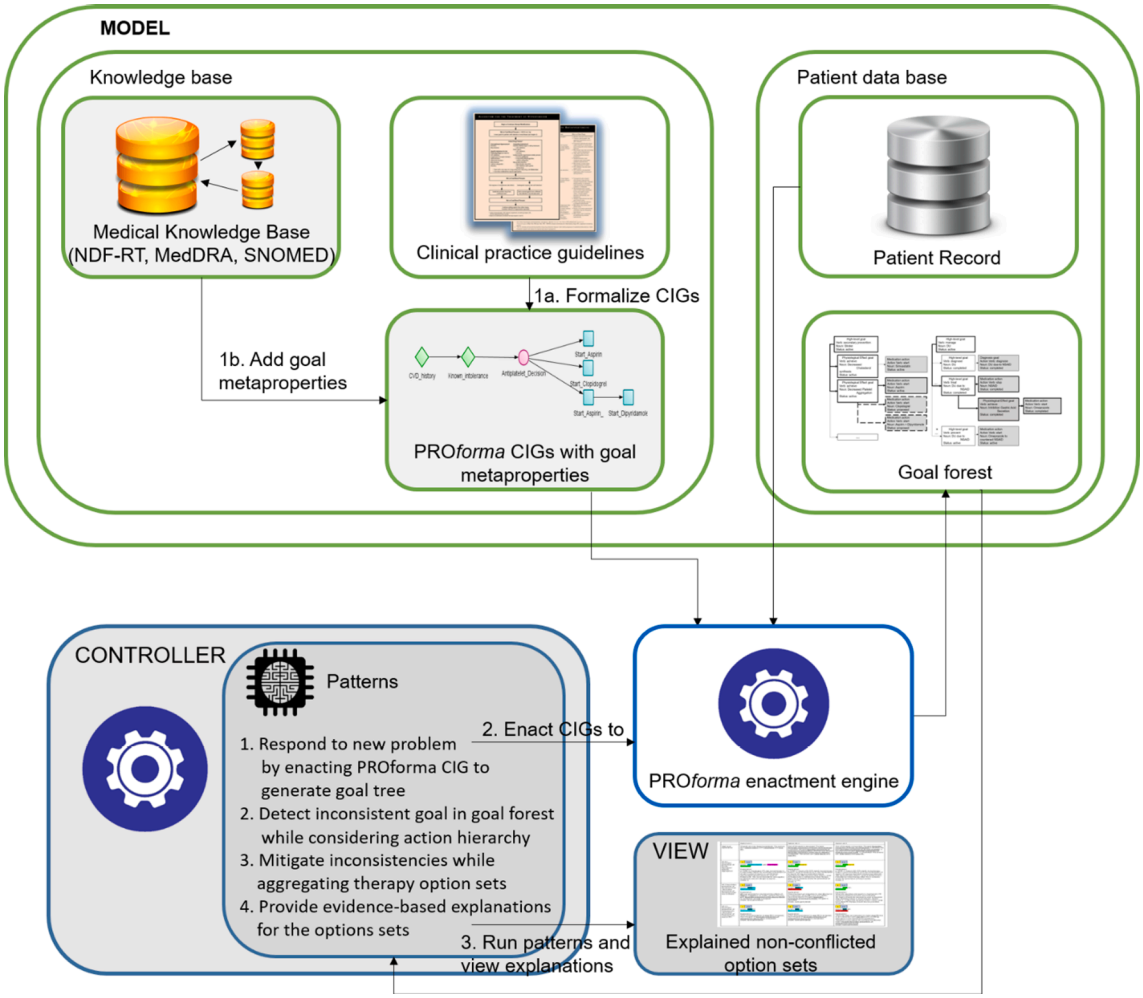


Fig. 1. GoCom's Architecture.

and against selecting a certain decision candidate are represented. This representation was also incorporated into EON and GLIF3. PROforma's TNM does not dictate a rigid flowchart control-flow, but instead tasks are assumed to act in parallel unless scheduling constraints are specified and are enabled if their precondition and scheduling constraints are met. PROforma tasks have optional metaproperties that allow expressing metadata associated with the task. This allows us to enhance the specification with additional information without the need to extend the PROforma formalism. Thus the clinical goals of tasks that GoCom uses for reasoning are encoded as PROforma task metaproperties. In addition, PROforma is supported by the commercial Deontics [14] authoring and enactment suite. For all of these reasons, we chose to rely on PROforma for CIG modeling and enactment for generation of goal trees.

An alternative CIG language that can support goal modeling is Asbru [15]. In Section 2.3 we discuss and contrast goal modeling in PROforma and Asbru.

2.2. Interaction between comorbid CIGs

The topic of detecting and mitigating interactions among CIG recommendations for comorbid diseases has started to be addressed in recent years [16]. In Table 1 we provide a comprehensive comparison among approaches. In Kogan et al. [7], we summarized the most prominent approaches. Below, we provide an aggregated analysis of the state-of-the-art approaches detailed in Table 1.

Many types of interactions have been observed, including repetition/redundancy, conflict, alternative, medication-interaction, medication generalization, different level of support for recommendations, different concept definitions, and temporal or sequential constraints between tasks. Mitigating such interactions can be done by choosing a non-conflicted alternative, scheduling tasks so that they do not interact, adjusting the dose, adding/removing/changing an action to mitigate the interaction, or allowing the interaction to occur and monitoring for adverse events.

The approaches differ with respect to the solution they offer (detection, composition of a potential care plan, verification), the formalism and type of reasoning used (e.g., OWL, logic programming), whether CIGs are represented as rigid flowcharts or allow action selection based on flexible argumentation, goals are considered and reasoned with, hierarchies of actions and controlled vocabularies are used, time is addressed, and whether the approach works just for two CIGs or for any number of CIGs.

Examining existing approaches, we can see that almost all of the examples that are used in these studies specify a rigid *flowchart* that specifies strict pathways of specific actions. See for example Fig. 2a for the Transient Ischemic Attack (TIA) CIG taken from [26] in which "start Aspirin" and "start Dipyridamole" are used instead of the more general "start antiplatelet" (the TIA CPG specifies indications for many antiplatelets including Aspirin, Dipyridamole, combination of the two, Aspirin with proton-pump inhibitor (PPI), and Clopidogrel). The CIG in [26] specifies a strict ordering that is not restricted by the original CPG and does not view Aspirin abstractly according to its physiological effect – antiplatelet –used for the goal of secondary prevention of cardiovascular disease (CVD).

Table 1
Comparison of approaches for detecting and mitigating interactions among CIGs for multimorbidity.

Author/ project name	Formalism	Reasoning	Action types	Action hierarchy	Interaction types	Goals	time	# CIGs	Vocabulary for actions & states	Detect conflict (D), Propose solution (S), Verify (V)	Action selection (flowchart/ argumentation)	Execution
Ten Teije and Pruski [17]	OWL + SPARQLCIG based on state transitions (Actions (not) recommended); CIG-independent interaction rules; DrugBank for interactions	Infer using SPARQL type of interaction between recommendations	Drugs	Drug hierarchies	RepetitionContradiction, Alternative, drug-interaction, drug generalization, opposed beliefs, redundancy	+ textual	–	≥2	DrugBank (or any other vocabulary) for actions	D, V	The case studies examined were flowchart-based (taken from [18 19])	SPARQL
Terenziani [2021] [22232425]	GLARE CIG language; OWL + SWRLIntentions ontology focus on body parts and modality (increasing/ dec); Interaction ontologyFocus on effects of drugs and temporal aspects of management (e.g., precise or imprecise, times, delays, durations)	Interactions detected; Backward navigation for alternative paths; Planning finds action set achieving intentions; Temporal reasoning	Any but considering drugs and intentions	ATC, SNOMED for hierarchies	Intention interactions (with type concordance, discordance, independence), drug interaction (effect's intention and modality)	+	+	2	ATC, SNOMED	D, S (partial – see last column)	Flowchart Rules for choice specified separately as interaction instances	Exploration of reconciliation alternatives
Wilk [2618272829]	FOL used to define adverse interactions and very specific mitigation operators (e.g., drug dose); Patient preferences, activity duration & offset. Precedence.	Constraint logic programming (CLP), PDDL (in [28]). Automatic calculation of temporality of mitigation operations	Any (no semantics)	–	Adverse interactions; Mitigation calculates how long to delay Tx due to overlaps	–	+	≥2	–	D, S, V	Flowchart (Activity graph)	CLP engine, PDDL
Zhang [30]	Like [18] but based on graph theory and Answer Set Programming (ASP)	Answer Set Programming	Any, no semantics	–	Same as Wilk	–	–	≥2	–	D, S, V	Flowchart	ASP engine
Fdez-Olivares [313233]	Hierarchical task network;Potential interactions represented as predicates	Agent planning generates non-conflicted plan; optimizing resource efficiency, action complexity	Any (no special semantics)	–	Drug-drug interaction, drug-disease contraindications, redundant intervention, timing interaction	+ no ontology	+	2	–	D, S	Flowchart	HTN Planner

(*continued on next page*)

Table 1 (*continued*)

Author/ project name	Formalism	Reasoning	Action types	Action hierarchy	Interaction types	Goals	time	# CIGs	Vocabulary for actions & states	Detect conflict (D), Propose solution (S), Verify (V)	Action selection (flowchart/ argumentation)	Execution
Abidi and Jafarpour [1934]	OWL (Web ontology language)-based CIG (state-transition model) + SWRL (Semantic web rule language) constraints	SWRL merging rules specifying Workflow Constraint, Institutional Constraint and Medical Constraint	Any (no special semantics)	–	identical tasks, simultaneous execution, conflicting tasks, temporal or sequential constraints btw tasks, task combination	–	+	2	–	S - manual specification ofconstraints specifying alternative for specific pair of comorbidities	Flowchart	OWL CIG engine
Riano [3536]	Hierarchical task network for CIG; Ontology: seriousness, evolution, acuteness of patient condition	Merging considers: acuteness, evolution and seriousness; Rules to add /delete drugs	Any [35] (no semantics) Drugs [36]	ATC for active principles	Drug-drug, drug-disease, drugs indicated for co-diseases;Mitigation rules add or delete drugs	–	–	2	ATC for actions	S in [36] but not at Wf level; simply activates rules that capture all needed changes	GLs not addressed, only concurrent drugs	Rules engine
Seroussi [37]	Extended GEM to note strength, character (dominant/ recessive), sign to rank recommendations	Eliminate redundancy &incoherence; rank; select by second morbidity goal	Any (no semantics)	–	Fusion of recommendations with equal character and sign; elimination of rec. with equal character and opposite sign	–	–	≥2	–	D, SFor a limited small case study	Single recommendations considered	Rule engine
GLINDA [38]	Ontology of GL interactions	Planned to prioritize and integrate recommendations after repairing interactions	Any (no special semantics)		Inconsistent goals, different concept definitions, drug-drug, timing, different support, contraind.	–	–	≥2	–	–	Flowchart or argumentation	Not implemented
Marcos [39]	PROforma CIG built from reusable components	Utilize a library of reusablecare plan components			Contraindications had to be elicited and added to the combined CIG	–	–	2	–	–	argumentation	Not implemented

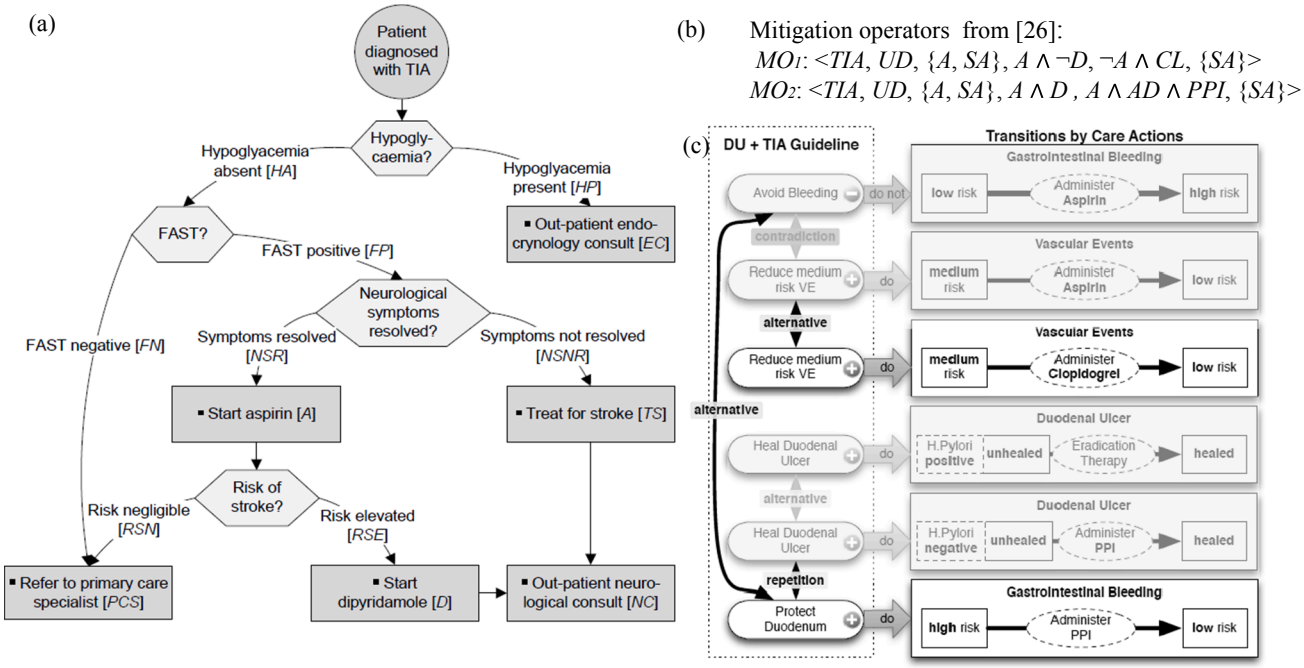


Fig. 2. (a) Transient Ischemic Attack CIG taken from [26]. (b) Mitigation operators used in [26] to solve the conflict between "start Aspirin" (A) and "stop Aspirin" (SA). D-Dipyridamole, CL-Clopidogrel. (c) Interactions model from [40].

In approaches based on flowcharts, interactions among specific actions (from a single CIG or multiple CIGs) are discovered and then mitigated (e.g., the Duodenal Ulcer (DU) guideline recommends stopping Aspirin which contradicts the TIA recommendation to start Aspirin). However, CPGs seldom list only single actions; rather they discuss alternatives for the same goal and provide knowledge for choosing among them. For example, the Stroke Prevention in Patients with Stroke and TIA [41] guideline indicates a high-level goal of CVD secondary prevention, for which a lower-level goal is the antiplatelet goal and specifies three alternative actions that meet this goal: aspirin, apririn + dipyridamole, or clopidogrel (See Fig. 2). Therefore, it makes sense that **the modeling of action choices should focus on a clinical goal, provide candidate actions that fulfill the goal, and provide the arguments for and against each candidate**. This is the approach that we have taken, which has been outlined in [7] (see Fig. 3). In this way, mitigating actions could be specified as part of the CIGs (e.g., replacing Aspirin with Clopidogrel or adding PPI to Aspirin + Dipyridamole, like in [26]). Furthermore, arguments from multiple CIGs, and possibly from additional sources of knowledge, could be used to plan a conflict-free intervention that fits the comorbidities of the patient. Such form of *goal-directed argumentation-based selection of decision-alternatives (actions)* is used in the PROforma [13] CIG formalism, which we build on. While Marcos and coauthors [39] have used this formalism in their study on comorbidity management, they have not considered action argumentation but have focused on reusable CIG components (i.e., structure consisting of admission, diagnosis, reassessment, and follow-up plans). None of the existing approaches (see Table 1 and Fig. 2b, 2c as prominent examples) use standard medical knowledge bases and commercial CIG engines, nor do they detect and mitigate interactions during CIG enactment. Moreover, many of the studies represent decision alternatives found in the CPGs as mitigation operators rather than as options of the original CIG, thus not doing justice to the CPGs and making the mitigation operators overly specific. Hence, clinical decision-making approaches still have to advance quite a bit before complete support for multimorbidity is achieved.

2.3. Goal modeling for CIGs

The PROforma CIG model uses the "domino model" [13,42] of the cognitive processes that take place throughout the dynamic decision-making cycle. In this model, an agent's beliefs about current circumstances (i.e., patient's current clinical state and ongoing medical-care actions) can lead to new goals; goals can lead to options for decision making, and options can lead to commitments (about what to believe or what to do) with an associated rationale; finally, a commitment can lead to adopting a plan, composed of actions [42]. Thus, high-level goals (such as diagnosis, treatment or prevention) may be associated with high-level plans. The high-level plans unfold as task networks that include lower-level plans which may include enquiry tasks to collect data used for diagnosis and decision tasks that allow users to select among candidate actions. All of these task types (plan, enquiry, decision, and action) may be associated with a goal (through their *goal* property) [13]. To further structure the goal, Fox et al. [43] categorize goals into knowledge goals or action goals. Knowledge goals associated with enquiry tasks acquire information about specific setting. Knowledge Goals associated with decision tasks are used to decide among alternative hypotheses about the world. Action Goals associated with plans or actions are used for achieving some state of the world or for enacting tasks. Goals are formulated as a verb and noun phrase (e.g., manage hypertension). Optional properties are used to specify restrictions (e.g., temporal constraints such as "within two weeks"), policy definition (obligatory or recommended), and rationale (text).

Grando et al. [4] presented a goal-oriented, hierarchical framework that aims to detect and prevent exceptions (namely adverse events) by linking the exceptions to goals and linking goals to plans or actions that can satisfy them. PROforma is extended using *keystone* tasks in order to model goals that are defined to have a number of states (e.g., "In Progress") and can be satisfied or unsatisfied. Goals are key objects in this system, as they are used to detect and mitigate exceptions via the exception manager that monitors the system in run-time, triggering relevant goals and using them to solve the situation.

In the Asbru CIG language [15,44] *intentions* (goals) play a major role in guideline validation and verification, application, critiquing, and evaluation. This may allow a system to determine whether the guideline

was correctly performed and had achieved its goal, and whether there are conflicts between different guidelines. Intentions are temporal patterns of actions (processes, such as monitoring blood pressure) and patient states (such as normal blood pressure), at different levels of abstraction, that should be maintained, achieved, or avoided during plan enactment or after it had ended. The syntax of the temporal annotations for the specification of intentions allows the representation of uncertainty in starting time, ending time, and duration of a time interval. These annotations may refer to a reference time point, which can be an absolute reference point, a reference point with uncertainty, a function (e.g., completion time) of a previously executed plan instance, or a domain-dependent time point variable [15]. In addition to intentions, the effects of plans may be specified in order to specify how the plan is expected to affect clinical parameters (e.g., the statin administration plan decreases cholesterol level, or the plan may decrease the dose of the medication) and how likely the intended effects may occur.

Peleg et al. [5] present an ontology that was developed using OWL and that supports reasoning with effects of clinical actions. The authors also show that the ontology can function as a source of general medical knowledge, providing clinical recommendations as well as explanations. Goal states (e.g., complete response) are used to define a guideline's goals. For example, when the goal is to administer a certain combination of medications in order to treat Amyloidosis (e.g., CTDAchieveCompleteResponse), the system is provided with the context diagnosis (e.g., AL-Amyloidosis), it then recommends the execution of the action of administering a combination of medications (CTD). When it is informed that the action was successful (e.g., has_effect some CompleteResponse), it can conclude that the desired goals has been achieved (e.g., desirable value true).

When making a choice between the alternative ways of representing goal in CIGs, the most robust formulations are those of Asbru and PROforma. Comparing goal specification in Asbru and PROforma, it is evident that Asbru has the advantage of temporal annotation. Temporal knowledge representation is necessary in many disciplines, including medicine, and it supports many important features (e.g., detection of patterns and trends) [45]. However, with the benefits that it brings, temporal modelling presents many challenges (e.g., outdated data, construction of temporal databases) that require complex implementation techniques.

In contrast, some of the goals of clinical guideline, in particular diagnosis goals, cannot be easily captured by Asbru. PROforma's formulation of goals was empirically derived by studying how goals are formulated in clinical guidelines. Hence, clinical goals found in clinical guidelines are easily translated into the verb and noun-phrase formulation of PROforma, as demonstrated in [43]. Moreover, the noun phrases can be taken from controlled terminologies (e.g., NDT-RT, SNOMED-CT), supporting standardization and knowledge sharing. As an example, "treat" is a term often used in clinical guidelines, and it is easy to map this term into the NDF-RT relation "may-treat" and into the verb "treat" in PROforma's formulation of goals. The translation of clinical goals into Asbru's ontological distinctions is not always easy due to the specific semantics that Asbru offers. For example, maintain and achieve are distinct alternatives in Asbru whereas achieving and maintaining a clinical parameter, such as blood pressure, are not distinguished in NDF-RT, which uses the relation "may-treat", which does not capture such specific meaning.

Considering the ease of translating clinical goals statements appearing in clinical guidelines into PROforma's formulation of goals and given that our current formulation is not focused on temporal modeling, we chose to follow the simpler PROForma semantics for this study. Rather, this study focuses on the complexities of multimorbidity conflict detection and mitigation, option set aggregation and explanation, and leaves the temporal aspect for future work. More details of possible future work on temporal knowledge representation is described in the Discussion section.

3. Methods

As mentioned in the Introduction, GoCom was developed following the Model-View-Controller software architecture pattern [6]. This section describes the methods used to develop (1) GoCom's Model – the data structure of the system, (2) GoCom's Controller's novel detection, mitigation and explanation algorithms that go beyond those reported in [7], and (3) GoCom's View, which presents results to clinicians.

3.1. GoCom's model

GoCom's Model is used to store and manage the Knowledge Base and the Patient Model that contains the patient-specific data and a patient-specific Forest of Goal Trees. The Knowledge Base includes CIGs encoded in PROforma and the NDF-RT drug ontology [10]. The Knowledge Base also includes a table that associates clinical conditions with relevant CIGs, which allows the Controller to find and run the CIG when a new condition is added.

3.1.1. GoCom's knowledge base

3.1.1.1. Goal-based modeling of PROforma CIGs. As stated in the Introduction, the generic and modular nature of our approach for allowing the Controller to semantically integrate recommendations from multiple CIGs and additional medical knowledge sources stems from the goal-oriented modeling of PROforma guidelines. The **goal-oriented modeling method** that we developed is an extension of the knowledge acquisition process for the Consensus Method defined by Shalom et al. [46]. The modifications span steps 1 and 3 of Shalom's Consensus Method and are described in detail in [47]. Here we provide a short summary. In [47], we also presented an experiment with nine third-year Information Systems students serving as knowledge engineers (KE), demonstrating the feasibility of modeling goal-oriented CIGs using our methodology that has 80% concordance with the gold-standard CIG specification.

3.1.1.1.1. Goal-oriented consensus Method for CIG knowledge acquisition. **Step 1**. The Consensus Method starts with clinicians selecting parts of guidelines that should be formalized as CIGs and adding annotations to make the document comprehensible to the knowledge engineers (KEs) who will formalize the guidelines. Annotations in our case, include adding names of specific medications where medication classes are specified (e.g., suggest a particular statin). This supports the KEs when they search medication ontologies to identify physiological effects of medications. Example of an informal consensus document produced in this step is shown in Fig. 3.

Step 2. The clinicians then answer the questions of the KEs about the annotated guidelines and the document is revised into an agreed-upon informal "consensus" document.

Step 3. The KEs select a CIG language and specify a formal consensus using the constructs of that language. Our modification [47] of Shalom's knowledge acquisition process includes a Guide that explains how to specify PROforma CIGs in a goal-oriented way. Guidelines encoded in PROforma have four types of tasks: enquiries, decisions, actions, and plans (high-level tasks that contain networks of lower-level tasks). The Guide that we developed includes templates for clinical tasks that are represented as diagnosis and management (treatment or prevention) plans (task networks). After specifying PROforma's task network structures for clinical processes, the Guide provides direction for defining goals using the task metaproperties of PROforma Plans and Actions, as detailed in the section below. An example of a goal-oriented CIG specification for the informal consensus shown on the top of Fig. 3 is shown in Fig. 4, created using the PROforma Alium tool.

Step 4. The clinicians and KEs validate the formal consensus.

3.1.1.1.2. Modeling of goals. Our goal-oriented CIG modeling approach augments the CIG specification with metadata containing

CVD 2º prevention [55][41]

Cardiovascular risk	Lifestyle	Drug Therapy	Treatment goals	Follow up
CVD risk clinically determined ≥20%* (Secondary prevention)	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, physical activity and smoking cessation interventions. Lifestyle advice should be given simultaneously with drug treatment	**In all patients:** Clopidogrel aspirin, or other antiplatelet drug if not tolerated/contraindicated ▪ intensive statin therapy **In all patients with CHD:** ▪ an ACE inhibitor *(see SIGN 96)* **Following MI:** ▪ a beta blocker *(see SIGN 93)* **With hypertension** *(≥140/90 mm Hg or > 130 mm Hg / > 80 mm Hg in patients with diabetes with complications or renal disease and target organ damage)* ▪ antihypertensive drug therapy	Aspirin – lifetime treatment with 75 mg/day Lipids – intensive lipid lowering therapy Simvastatin BP – treat to reduce to < 140 mm Hg systolic and/or < 90 mm Hg diastolic Lisinopril	Risk factor monitoring every three to six months

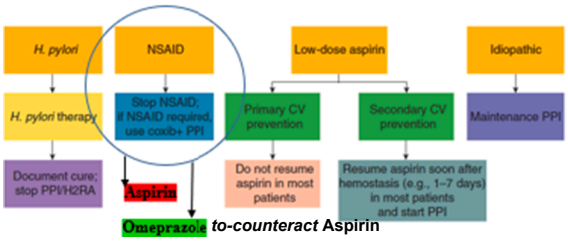
CVD 2º prevention. Decreased Platelet Aggregation

A **Individuals with established atherosclerotic disease should be treated with 75 mg aspirin daily.**

☑ Clopidogrel should be considered in patients with symptomatic cardiovascular disease who have aspirin hypersensitivity or intolerance or in whom aspirin causes unacceptable side effects.

A **Individuals with a history of stroke or transient ischaemic attack and who are in sinus rhythm should be considered for low dose aspirin** *(75–300 mg daily)* **and dipyridamole** *(200 mg twice daily)* **to prevent stroke recurrence and other vascular events. If aspirin is contraindicated, or there are side effects, clopidogrel 75 mg daily is an alternative.**

Treatment and secondary prevention of DU due-to NSAID [56]



Osteoporosis Diagnosis [48]

Post-menopausal patients should be evaluated for osteoporosis. This is done using Fracture Risk Assessment Tool (FRAX) and bone mineral density assessment via axial dual-energy X-ray absorptiometry. When osteoporosis is established, the patient should be evaluated for causes of secondary osteoporosis (see Table 11 in [48]). Laboratory evaluation should include a complete blood count (CBC); comprehensive metabolic panel; Serum 25-hydroxyvitamin D, intact parathyroid hormone (PTH); phosphate; and a 24-hour urine collection for calcium, sodium, and creatinine. If the patient is receiving thyroid hormone or there is a suspicion for hyperthyroidism, thyroid-stimulating hormone should also be measured. If there is clinical or biochemical evidence of malabsorption, celiac antibodies should be obtained. Serum and urine protein electrophoresis could be obtained if there is a suspicion for multiple myeloma (e.g., non-PTH mediated hypercalcemia).

Osteoporosis Treatment /prevention

If the patient is taking a drug (e.g., PPI) known to be a contributing factor to osteoporosis (see Table 11 in [48]), consider stopping that drug.
Patients with high risk for future fractures (>=20%) should be given medications to reduce the risk: alendronate, risedronate, zoledronic acid, or denosumab[3].

Fig. 3. Informal consensus documents of the Cardiovascular Disease (CVD), Duodenal Ulcer (DU), and Post-menopausal Osteoporosis CPGs.

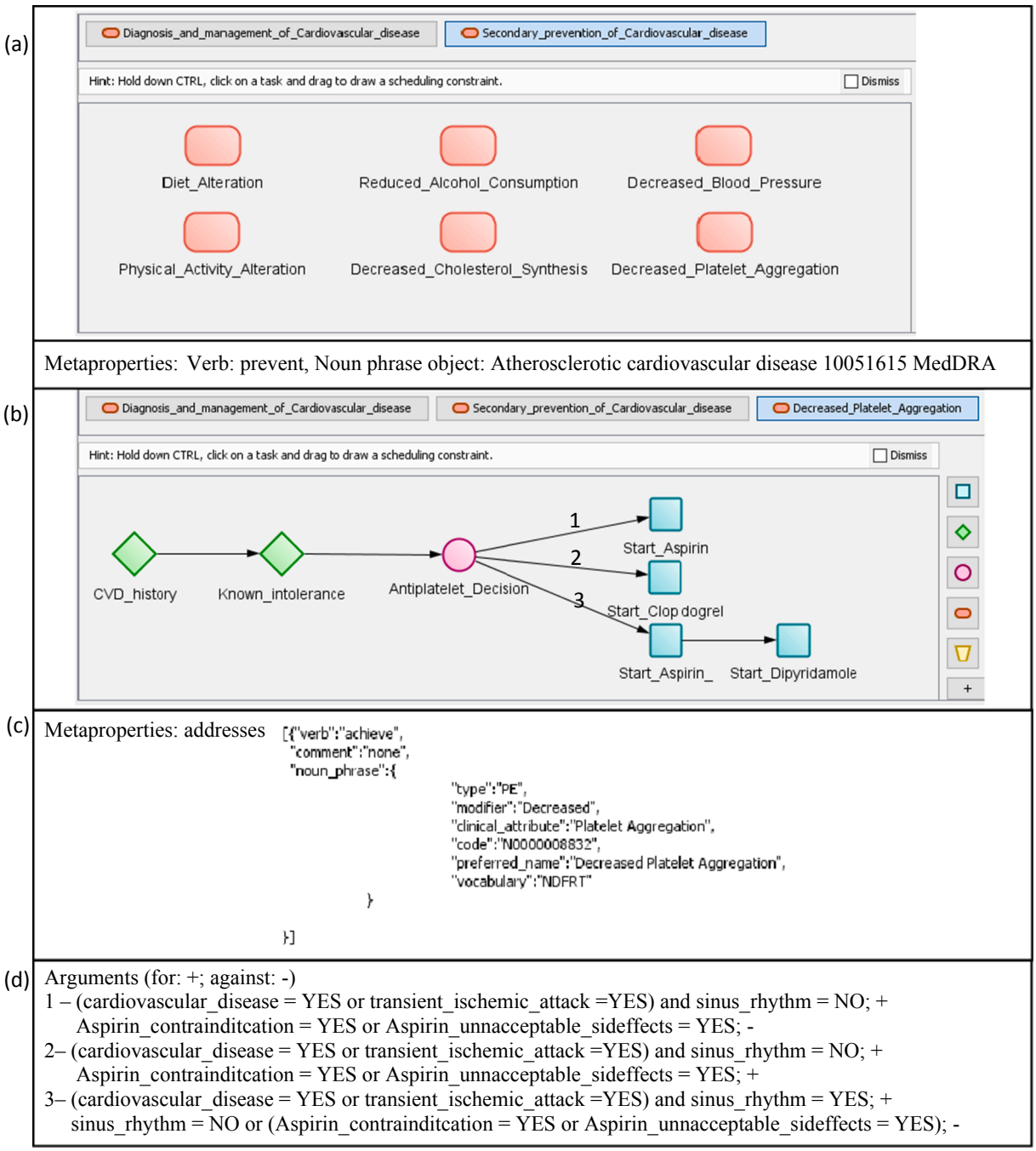


Fig. 4. CVD CIG corresponding to the consensus shown at the top of Fig. 3. (a) secondary prevention of CVD plan includes six subplans and goal metaproperty. (b) details of the Decreased Platelet Aggregation plan. The tasks that make up this plan include two enquiries that collect patient information, followed by a decision among three different antiplatelet medications. (c) shows the metaproperties information for the physiological effect goal "Decreased Platelet Aggregation". The JSON object is an ADDRESSES_OBJECT. The JSON object that follows "noun_phrase" is-a Atomic_PE_NP. (d) shows the PROforma arguments for the Antiplatelet Decision that determines which action-enactment goal will be selected.

controlled terminology terms to facilitate the mapping of CIG decision arguments to patient data and to support the goal-based reasoning process for detecting and mitigating inconsistencies (see Section 3.2). This approach integrates modeling ideas from an ontology of goals by Fox et al. [43], relationships found in the NDF-RT ontology, and FHIR's Goal resource.

A formal definition of goals

In GoCom, we specify the state of the world (initial as well as desired) as a structure consisting of the patient's information, a set of goal trees (Goal Forest) and a set of inconsistencies between goals. Below we provide formal definitions of these concepts. Non-technical readers may read the two paragraphs below on Goal Subtypes and move on to Section 3.1.2.

Definition 1.. *A **State of the world** can be defined as the following tuple: $<PI, G_{forest}, IN>$, where:*

PI *= {PD, O, P, MR, PR, E}. A set of data items recording the Patient's information, contained in the patient's record that is based on FHIR classes, including the sets of the Patient's demographics (PD), Observations (O), Conditions (P), Encounters (E), as well as Medication Requests (MR) or Procedure Requests (PR).*

$\boldsymbol{G_{forest}}$*: The patient-specific goal forest consists of goal trees* $\{G_{tree_1}$,

*G_{tree_2},…G_{tree_n}}, each of which is a tree structure composed of **GOAL_NODEs** (see Definition 2). The relationship among child nodes are XOR or AND, depending on the way the tasks are specified in the PROforma CIG.*

***IN**: A set of inconsistent goal-node pairs and the goal forest in which they occur in the system {IN_1, IN_2,..IN_n}. In the desired state, this set is empty.*

Goal subtypes

Fox et al. [43]'s ontological specification of goals distinguishes between Knowledge Goals, which help acquire information or make decisions about alternative states of the world, and Action Goals that either enact a task or achieve some state (e.g., achieve Decreased Platelet Aggregation). We chose to distinguish among five subclasses of goals: Diagnosis Goal (a Knowledge Goal), Action-enactment Goal, and three State-achievement Goals: Treatment Goal (to achieve the state where problems have been treated), Prevention Goal (to achieve the state where prevention actions have been taken), and Physiological-Effect Goal (to achieve some physiological state). The first four are common in medical practice and the last one, Physiological-Effect Goal, is inspired by NDF-RT's relationship "Pharmaceutical Preparation has_PE Physiological Effects", where a Physiological Effect is a state (e.g., Decreased Platelet Aggregation). Fig. 5 provides the Class Diagram of the five goal types along with examples.

It is important to note that during clinical decision-making, we start with more abstract goals of diagnosis, treatment, or prevention. We can then specialize the treatment or prevention goals (e.g., secondary prevention of cardiovascular disease – see Fig. 4) by focusing on the desired physiological effect (e.g., achieve Decreased Platelet Aggregation) and finally select an appropriate action-enactment goal (e.g., start Aspirin, start Clopidogrel) that would accomplish the physiological-effect goal. In general, we try to rely on the guidelines and clinical research to specify the intermediate physiological effects. However, sometimes the guidelines are not clear on the physiological basis for the use of the medications, and we need to consult expert physicians or additional references.

Definition 2.. *A **GOAL_NODE** is a tuple < ID, PG, LS, D, ADDRESSES_OBJECT>, where:*

***ID**: ID of the goal node*

***PG**: The parent goal node of the current goal node*

***LS** ∈ {proposed, accepted, rejected, active, on-hold, completed, cancelled}. The goal's life-cycle status corresponds to the lifecycleStatus attribute of the Goal class in the FHIR model. This attribute propagates the goal through its various states, and thus helps the Controller reason about the state of the goal in the system.*

***D**: The description attribute is used to store the CPG's recommendations for action-enactment goals (see subsection on goal sub-types above), including their level of evidence*

***ADDRESSES_OBJECT**: a specification of issues addressed by the GOAL_NODE.*

Definition 3.. ***ADDRESSES_OBJECT**: (V, NP). The intended meaning (see Fig. 4c) is similar to that of the FHIR "addresses" attribute. This attribute refers to issues addressed by the Goal resource, including Conditions, Observations and Medication Statements. Per the goal ontology of Fox et al. [43], we specify the goal in terms of a verb **V** and a noun phrase **NP**. The ADDRESSES_OBJECT is expressed in JSON syntax. Fox [43] does not address how goals should be represented as part of the PROforma specification. We chose to specify the verb and noun phrase as metaproperties of tasks of type Plan (for State-achievement Goal) and Action (for Action-enactment Goal). The metaproperty objects are specified using JSON syntax.*

***V** ∈ {start, stop, achieve, avoid, diagnose, treat, prevent, prevent_primary, prevent_secondary}*

The verbs "start" and "stop" are used for Action-enactment goals (e.g., start Aspirin). The verbs "achieve" and "avoid" (e.g., achieve Decreased Platelet Aggregation) are used for State-achievement Goals. The verb "diagnose" is used for Diagnosis goals. The verb "treat" is used for Treatment goals. The last three verbs are used for Prevention goals.

***NP**: the noun phrase part of the ADDRESSES_OBJECT,*

Definition 4.. ***NP**, a noun phrase, is an abstract superclass of ATOMIC_NP and COMPLEX_NP. Every NP has a TYPE.*

***TYPE**: Problem (P), Medication Request (MR), Procedure Request (PR) – based on FHIR, or Physiological Effect (PE), based on NDF-RT.*

Definition 5.. ***ATOMIC_NP**, a NP addressing a single medical concept, is a tuple < TYPE, CODE, PREFERRED_NAME, VOCABULARY>, where*

***CODE**: a vocabulary code*

***PREFERRED_NAME**: a string representing the preferred name of a concept*

***VOCABULARY**: the vocabulary from which the code and preferred name of a concept are derived. Codes and preferred names for physiological effects as well as medications are taken from NDF-RT, codes for procedures are taken form SNOMED-CT, and codes for diseases / findings are taken from MedDRA[1]. We use the MedDRA vocabulary to facilitate a connection to the AEOLUS (Adverse Event Open Learning through Universal Standardization) database [44], as part of our future work. The reference to these vocabularies allows the Controller to perform reasoning regarding medication subsumption. The NDF-RT was downloaded from Athena, a web based resource created by OHDSI and was integrated with the patient model in PostgreSQL [49].*

Example: (type: MR, preferred_name: Aspirin, code: N0000145918, vocabulary: NDF-RT).

Definition 6.. ***ATOMIC_PE_NP**, an **ATOMIC_NP** referring to a Physiological Effect, is a tuple < TYPE, CODE, PREFERRED_NAME, VOCABULARY, MODIFIER, CLINICAL_ATTRIBUTE>, where the NP's preferred name is also broken into a modifier and a clinical attribute:*

***CLINICAL_ATTRIBUTE**: represents the core clinical attribute of a PE. For example, in "Decreased Platelet Aggregation", the clinical attribute is "Platelet Aggregation".*

***MODIFIER** ∈ {Decreased, Increased, Inhibition, Stimulation, Suppression, Negative, Positive, Depolarization, Repolarization, Vasoconstriction, Vasodilation}.*

The MODIFIER modifies the clinical attribute of a PE. For example, in the "Decreased Platelet Aggregation" PE, the modifier is "Decreased". The modifier and the clinical attribute are extracted from the Physiological Effect NP, and the modifiers are paired (see Definition 8) in order to detect conflicts between Physiological Effect Goals (e.g., Increased Platelet Aggregation vs. Decreased Platelet Aggregation).

Example: (type: PE, preferred_name: Decreased Platelet Aggregation, code: N0000008832, vocabulary: NDF-RT, modifier: "Decreased", clinical_attribute: "Platelet Aggregation").

Definition 7.. ***COMPLEX_NP**, is a tuple < np_1, RELATION, np_2 >, where np_1, np_2 are instances of NP, and*

***RELATION** ∈ {due-to, to-counteract}*

In the case of "due-to" relation, np_1 is a NOUN_PHRASE whose type is Problem and np_2 is a NOUN_PHRASE whose type is P, MR, PR, or PE. For example, Duodenal Ulcer due-to NSAID.

In the case of "to-counteract" relation, np_1 is a NOUN_PHRASE whose type is MR and np_2 is a NOUN_PHRASE whose type is MR. For example, PPI to-counteract Aspirin. These two relations are used by the Controller's reasoning algorithm to mitigate certain types of Adverse Events.

Definition 8.. *An **Inconsistent goal-node pair** in a goal forest occurs when two goal nodes have inconsistent verbs or modifiers but refer to the same noun phrase object either directly (e.g., both refer to Aspirin) or through subsumption (e.g., one goal refers to Aspirin and the other goal refers to NSAID, and it is determined that Aspirin is-a NSAID).*

IN_i = ($GOAL_NODE_1$, $GOAL_NODE_2$, G_{forest}) where $GOAL_NODE_1$ has an ADDRESSES_OBJECT (V_1, NP_1) and $GOAL_NODE_2$ has an

[1] The NDF-RT drug ontology provides its own code IDs but also refers to SNOMED-CT for procedures, and MedDRA for problems.

ADDRESSES_OBJECT (V_2, NP_2) *and* (V_1,V_2) ∈ *VERB_and_MODIFIER_PAIRS and* NP_1 *equals or subsumes* NP_2.

Inconsistent verbs are defined as pairs of verbs:

VERB_and_MODIFIER_PAIRS = {(*start*, *stop*) | (*achieve*, *avoid*) | (*Decreased*, *Increased*) | (*Inhibition*, *Stimulation*) | (*Suppression*, *Stimulation*) | (*Negative*, *Positive*) | (*Depolarization*, *Repolarization*) | (*Vasoconstriction*, *Vasodilation*)}.

G_{forest} *is the goal forest in which the inconsistent goal-node pair occurs*.

Definition 9.. *A management* ***option set OS*** *is a collection of non-conflicting management plans* (*goals and the associated actions*), *together with their explanations*, *that a user can choose to manage a multmorbidy patient. More formally*: ***OS*** *is a consistent conjunctive goal forest constructed by GoCom*, *such that*:

(1) *there does not exist any inconsistent goal-node pairs in the goal forest*,

(2) *siblings in the goal forest are conjunctive* (*i.e.*, *defined by the AND relation*),

(3) *nodes in the goal forest are either in the goal forest of the initial state of the world or nodes proposed by GoCom*,

(4) *leaf nodes that have active goals hold medications or medication groups enactment goals*,

(5) *nodes in the goal forest have lifecycle states updated or proposed by GoCom*. (*Thus*, *for example*, *a medication that had been started could be stopped by GoCom*).

(6) *there is an overall explanation for the goal forest and explanations for the leaf nodes*. *They are generated by GoCom's Controller based on the attributes of the goals*.

3.1.2. GoCom's patient model

The Patient Model includes the Patient's Record, the Goal Forest, and user sessions. Unlike the Knowledge Base, which contains information that can be used for patient populations, the Patient Model is patient specific. The Patient Record and Goal Forest are discussed below. The user sessions contain the responses of the clinician user to questions posed by the GoCom system for the purpose of system evaluation.

3.1.2.1. The patient record. This study used simulated patient data; real data would be used in future work and would be exported from medical institutions in a format that conforms to HL7 FHIR. In our current implementation, we directly create instances of patient data in GoCom's Patient Record. This Patient Record is realized as instances of FHIR [9] classes and is implemented in PostgreSQL using Fhirbase [50], stored on the Amazon Relational Database Service PostgreSQL server [51]. We store a table for each of the following FHIR classes: Condition (Problem), Observation, Goal, Medication Request, Procedure Request, Patient, and Encounter. These tables have the FHIR attributes of the respective classes. In addition, the Medication Request and the Procedure Request tables links via the reason_reference attribute to the Goal for which it was prescribed. The tables are used for the Controller's reasoning as described in section 3.2 as well as for retrieval of patient information for the View, as described in section 3.3.

To integrate with PROforma's item/value data model, the Patient Record transforms patient data into data items that are treated uniformly by PROforma; GoCom sends the information about the data items and their value, the guideline ID and patient ID as JSON objects (e.g., {"item":"Aspirin_unacceptable_side-effects", "value":"no", "guideline":"Stroke","patient_id":"125"}.

3.1.2.2. The goal forest. The Goal Forest (see Fig. 6 for an example) captures the current state of the patient's problem-oriented clinical goals and the suitable CIG-based interventions for meeting the goals. When a new event (i.e., problem/condition, medication request, procedure request, or clinical goal) is entered into the Patient Record, the Controller is triggered and activates the PROforma enactment engine to apply the respective CIG to the patient's data and generate the goal tree for the new condition (e.g., duodenal ulcer, gall stones, etc.). The PROforma CIG represents the clinical guideline's indications and contraindications for the various interventions as PROforma arguments for and against the different interventions. Based on the patient's current condition, the different CIG options are evaluated by the engine, taking into account all arguments instantiated per the patient's medical record. The indicated options are presented to the clinician, along with the arguments. The clinician then selects the option that the engine flags as the most preferred, or one of the other indicated options. These are committed into the goal tree (choice of goal leaf). Thus, the Goal Tree represents the current state of the active goals and management plans (action-enactment goals) for a single condition.

The tree structure represents goal/subgoal relationships between the patient's goals, going from more abstract goals (e.g., secondary prevention of stroke) to lower-level state-changing goals (Decreased Platelet Aggregation) and finally to Action-enactment goals (e.g., start Aspirin).

As additional conditions are entered into the Patient Record, additional goal trees are generated by GoCom, based on the PROforma engine's enactment of the respective CIGs. Before presenting the indicated options to the clinician, GoCom traverses the other trees in the multimorbidity Goal Forest to check whether the recommendations from the new CIG are conflicted with recommendations committed by the clinician in one of the other Goal Trees of the patient (for his older conditions). This helps GoCom in recommending only options that are not conflicted with the patient's current condition.

The tree structure of the goals is used by the Controller to detect and resolve conflicts arising from the new events entered into the Patient Record. Using a what-if look-ahead reasoning mode, the Controller simulates alternative future-forests without the need to make a single management choice and wait for its consequences. Each future forest represents an alternative mitigation plan that is consistent with the multiple CIGs and free of conflicts.

The mitigation plans are presented as alternative option sets. Each option set addresses the multimorbidity goals concurrently by presenting a management option for each concurrent goal. The options belonging to a set of goals are not conflicted. Thus, the different option sets present alternative non-conflicted management options that could be considered for the multimorbidity patient. Leaf management options contain recommendations to stop or start particular medications. The option sets are presented to the clinician user, along with explanations. The explanations summarize for each option set whether all goals are met or in cases some goals are not met, indicates this. This helps clinicians select option sets that are not only non-conflicted but also address all current goals. When the clinician chooses one of the option sets, the forest is updated to include the respective future forest.

Note that all interventions have potential adverse events, but they may not happen for a particular patient. If an adverse event occurs and enters the system as a new problem, the Controller has a new goal of mitigating the adverse event. In its mitigation reasoning, the Controller can back track from condition to condition, revisiting earlier decisions, using the "to-counteract" relationship in the goal forest. This relation represents the fact that a second medication was given to counteract the adverse effect of a first medication (e.g., omeprazole (medication 2 suggested by the DU guideline) *to-counteract* Aspirin (medication 1 suggested by the CVD guideline) – see bottom of Fig. 6b). Using backtracking reasoning, the Controller may recommend changing the clinician's previous choice to a different option that is not associated with the adverse event that has occurred. This option, along with the other non-conflicted option sets, are presented to the clinician along with explanations. Section 3.2.2 details a complex scenario of a patient in which three conditions occur over time, two being adverse events of prior management plans.

Technically, the Controller builds the tree by retrieving back, from the PROforma engine, the tasks that were enacted, according to the results of the decision tasks, as well as the metaproperties of the tasks. The information from the PROforma metadata (goal verb and goal noun

phrase) is translated by the Controller (see Section 3.2.1) into attributes of tree nodes. As an example, the CIG shown in Fig. 4 is translated into the Goal trees shown in Fig. 6(a).

A life-cycle status attribute records the current state of each goal. The possible states are taken from FHIR's lifecycleStatus attribute of the Goal class. Fig. 7 shows a state-transition diagram explaining how the clinician user responds to GoCom system recommendations that change the life-cycle status of the goals. GoCom proposes new goals, which are accepted or rejected by the clinician. Accepted goals become active if they persist over time; otherwise they are completed instantaneously[2]. From the active state, GoCom may propose management option sets that consider the multimorbidity and which may suggest to keep the goal, suspend it, cancel it, or complete it, if it is no longer necessary (e.g., if a medication was given to counteract the adverse effect of another medication and that medication has been cancelled). Goals that are rejected, cancelled, or completed can no longer change their state. However, similar goals can be proposed again by the CIG if the patient's state changes and decision support for the goal is rerun.

Apart from the main Goal Forest that reflects the patient's current state, we also keep Temporary Goal Forests which are alternatives generated and considered during mitigation (as described in Section 3.2.4).

3.2. Methods for developing and specifying the Controller's novel reasoning capabilities

We view the task of generating consistent recommendations for the management of a multimorbid patient as a planning problem that can be formulated as a tuple consisting of an initial state of the world, a new problem (clinical condition) that enters the system, and a set of pairs that consist of a desired state of the world and an option set that will help achieve it. Because the goals for managing a multimorbid patient may be inconsistent (see Definition 8) or some goals may require actions that make other goals unsatisfiable, there may be multiple possible desirable states depending on the choice of goals to satisfy.

Formally, the planning problem tuple is described as:

$<SI, P_x, \{(OP_i, SD_i)_{i=1..n}\}>$, where:

SI: The initial state of the world that exists before a new problem (condition) is detected.

$\mathbf{P_x}$: A new problem corresponding to the FHIR Condition (Problem) class that is detected.

$\mathbf{\{(OP_i, SD_i)_{i=1..n}\}}$: a set of pairs, consisting of an option set $\mathbf{OP_i}$ representing one of the alternative solutions proposed by the Controller's algorithm, along with the desired state $\mathbf{SD_i}$ that will result from choosing this particular option set.

A desired state of the world is a state where all the multimorbidity problems of the patient (in $SI \cup P_x$) have associated goal trees and the active goals of these goal trees are satisfied (i.e., their leaves contain active Action-enactment Goals), and there are no inconsistent goal node pairs. Therefore, an option set satisfies the multiple goals of a multimorbidity patient.

To solve the planning problem, the Controller implements an algorithm that respond to events (e.g., new problem (condition) for the patient that has been entered by the clinician user), while consulting the Knowledge Base and activating the API of PROforma's enactment engine. Patterns are also used to detect inconsistency and mitigate inconsistencies between the guideline recommendations' goals and medical actions. As in [7], we used Sequence Diagrams [52] to analyze and characterize the desired behavior of the Controller and its interaction with the Model and View components as it (A) responds to events (new medical problem, medication request, procedure request), (B) checks consistency between goals, while (C) resolving subsumption relationships between medications based on the NDF-RT ontology, (D) mitigates inconsistencies by (E) delivering sets of recommendations that are ***aggregated*** from several CIGs and are presented as management option sets (see Definition 9), where each option set contains non-conflicting recommendations so that the patient will be well managed, (F) generating explanations.

The Sequence Diagram analysis defines the Controller's behavior that we specify formally as algorithms and implement in Java. Patterns A and B were already presented in [7]; Pattern B was updated to check inconsistency between start/stop Action-enactment goals that refer to medications at different levels of granularity via ontological subsumption hierarchy. The high-level pattern shown in Fig. 8 provides the top-level algorithm of the Controller that activates the behavioral patterns and strategies.

The high-level Controller's algorithm of Fig. 8 starts when a new problem (e.g., diagnosis for the patient) is entered[3]. Once the guideline associated with the new problem is run, with the patient's data items, and the guideline tree is retrieved, consistency is checked among all the trees of the current problems (conditions) of the patient. Consistent recommendations are presented to the clinician user first, and then inconsistent recommendations are presented. After the clinician has chosen the relevant recommendations, consistency is checked again.

Line 9 of the high-level Controller' algorithm presents a while loop. However, infinite loops are impossible in the system because a medication that was replaced cannot be suggested again and thus the algorithm could never loop back into old solutions, making the solution-set final.

3.2.1. Detection of inconsistent goal-node pairs

Currently, GoCom can detect two types of inconsistent goal-node pairs (see Definition 8). The first type of inconsistency relates to medications that have opposed physiological effects. When goal trees include medication leaves (action-enactment goals), these leaves have parent goals that describe the desired physiological effects. The physiological effect goals have VERB_and_MODIFIER_PAIRS taken from the NDF-RT ontology (see Definition 6). Three examples of physiological-effect goals are shown in Fig. 6: decreased platelet aggregation, decreased cholesterol synthesis (Fig. 6a), and inhibition of gastric acid secretion (Fig. 6b). These physiological effects goals are inconsistent with increased platelet aggregation, increased cholesterol synthesis, and stimulation of gastric acid secretion, respectively.

The second type of inconsistency refers to opposed verbs on interventions: starting or stopping the same intervention or interventions that are in the same subsumption hierarchy, and is described in the next subsection.

The algorithm implemented in GoCom and presented in Fig. 9 can identify these two types of inconsistencies.

3.2.2. Resolution of action granularity based on subsumption hierarchies

Our goal-based framework works with conditions that evolve over time. As explained in Section 3.1.2.2, the initial goal forest reflects the current active goals that were selected by the clinician from a set of mitigated conflict-free option sets. The active goal trees have leaf nodes that refer to specific medications prescribed by the clinician) rather than medication groups). As a new condition arises, a new goal tree is derived from the CIG and is added into the goal forest. Leaves of this new goal tree may suggest starting or stopping a specific medication (e.g., Aspirin) or a more general medication group (e.g., NSAID), depending on how a recommendation is formulated in the CIG.

Recognizing inconsistent start/stop recommendations that relate to

[2] The enactment goal of stopping a medication is completed instantaneously if it is accepted.

[3] Our system can handle two new problems at the same time by running the CIGs iteratively, constructing a new tree from the two new goal trees returned from the PROforma engine (step 2) and adding it to the goal forest. All other parts of the algorithm will remain the same.

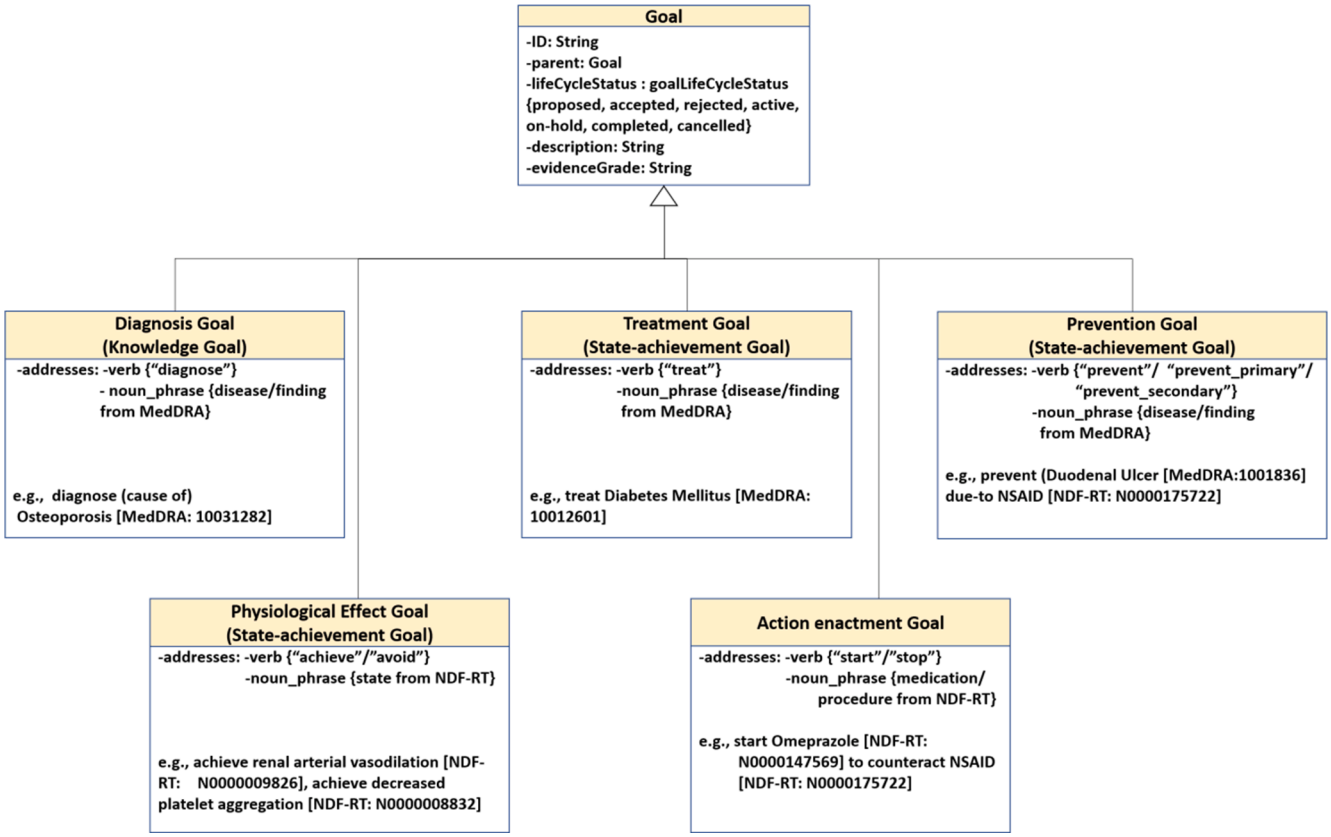


Fig. 5. Goals subclasses.

the same concept is straight forward. However, clinical guideline recommendations may refer to more abstract medication groups. For example, the stroke prevention guideline may recommend starting Aspirin and a patient may develop DU as an adverse effect of that medication. In turn, the DU guideline may recommend stopping NSAIDs (Non-steroidal anti-inflammatory medication), which is a medication group that includes Aspirin.

The Controller's consistency checking pattern (Pattern B, shown in Fig. 9) searches for inconsistency when a new leaf goal recommends stopping a medication, stop-M_2 (specific medication or medication group). If there exists an active start-medication goal, start-M_1, that refers to a medication M_1 (e.g., Aspirin), where $M_1 = M_2$, or if $M_1 \subseteq M_2$ (medication group M_2 subsumes specific medication M_1) then an inconsistency is detected (see Line 6 in Pattern B shown in Fig. 9).

Note that the parent goal node of the existing medication request, start-M_1, may not necessarily conflict with the new recommendation stop-M_2. For example, if the patient was prescribed Aspirin (M_1) as an Antipyretic (physiological effect goal) to manage fever (high-level goal), developed a DU, and the new proposed goal is to treat DU by stopping Aspirin (M_2), then the Controller's mitigation algorithm may indicate to stop Aspirin and select a different Antipyretic.

Subsumption is determined according to the terms of the NDF-RT terminology. We are using the Athena OHDSI Vocabularies Repository that provides the NDF-RT as relational tables. The "concept_relationship" table provides subsumption hierarchies with the relationship types "Subsumes" or "Is a" (for the reverse relationship). For example: Nonsteroidal Anti-inflammatory Drug (NDF-RT ID N0000175722) **Subsumes** Aspirin (NDF-RT ID N0000145918). Detected inconsistencies are saved in a temporary Java array list (Lines 7–8).

3.2.3. Strategies for mitigation of inconsistencies while aggregating therapy options for multiple clinical goals

Multimorbidity patients have multiple clinical goals for which GoCom tries to find consistent management plans, based on the options provided in the CIGs. After creating a new goal tree matching a new diagnosis, goal consistency is checked. Consistent therapy options do not need to be mitigated and are presented to the clinician before the inconsistent goals are mitigated by the Controller.

The Controller's mitigation algorithm uses a what-if approach that plans alternative goal forests for the multimorbidity patient. Each goal forest presents a non-conflicted therapy option set addressing all concurrent clinical goals of the patient that are involved in an inconsistency. To find option sets that meet all goals, the mitigation algorithm searches for alternative actions meeting the same goal by rerunning the CIG from its decision task associated with that goal. In cases where the action was started **to counteract**[4] the effect of an earlier action, the algorithm searches for alternatives for the early action as well (Fig. 10, lines 20–24).

Because meeting all goals simultaneously is not always possible, the option sets suggested by the aggregation algorithm may include an imperfect solution that discards some goals. The clinician may then decide which option set he or she prefers. Sometimes discarding a goal of lower priority may be preferable to a solution where, even though all goals are met, a less effective treatment is used to satisfy a high-priority goal.

The mitigation of inconsistencies is handled by addressing all pairs of conflicted goals in an iterative manner. For each inconsistency, two sides of the inconsistency are mitigated and alternative solutions are found. Additional inconsistencies may be added in the mitigation process if a proposed change to an enactment goal creates a conflict with the other goal in the inconsistent node pair being mitigated or if an enactment goal was started to counteract the effect of another intervention. The

[4] This is specified in the goal forest derive from the complex noun phrase Omerprazole (PPI) to-counteract NSAID

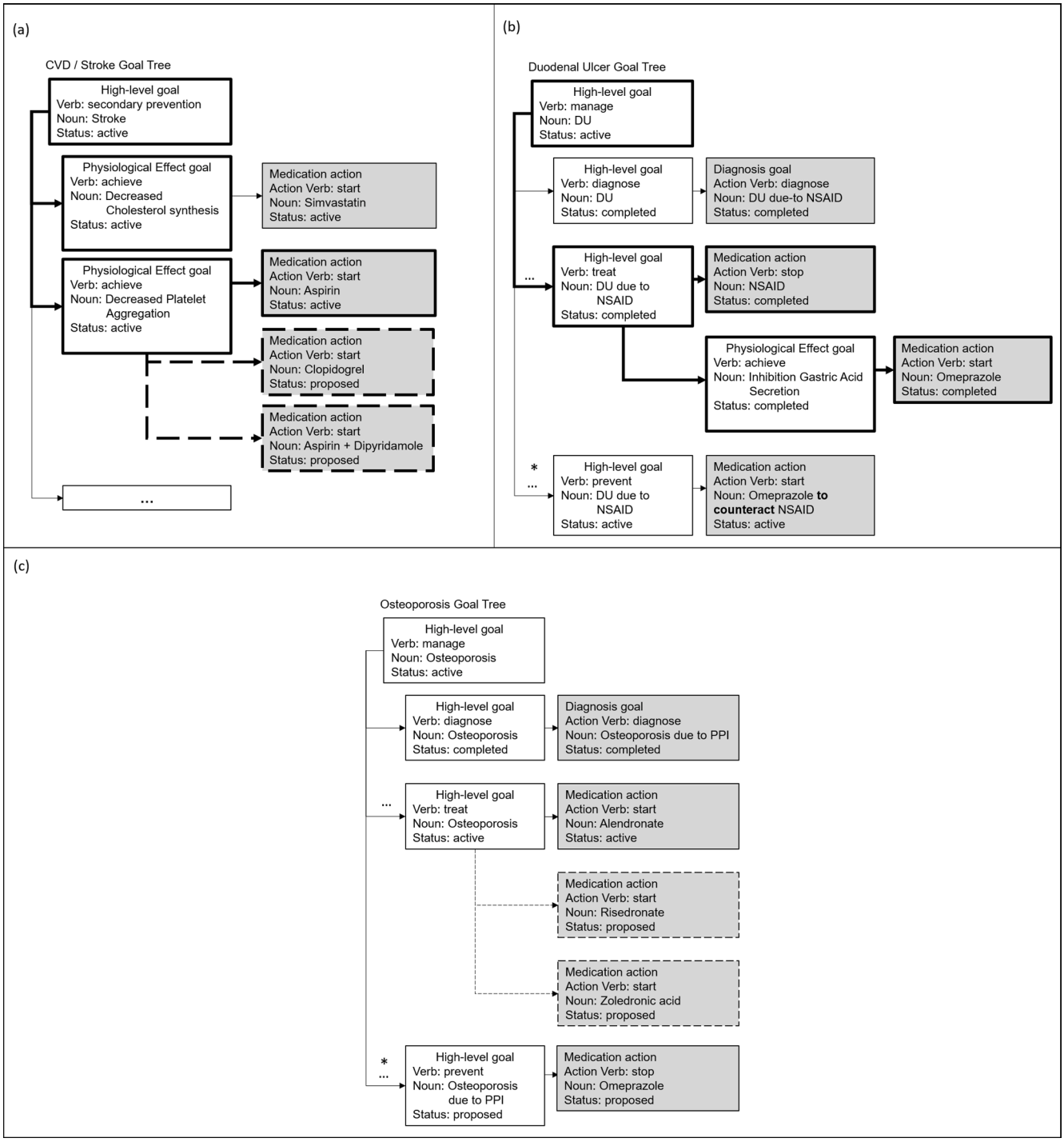


Fig. 6. Goal Forest for a patient who developed DU as a side effect of Aspirin, provided for secondary prevention of stroke / CVD. The PPI resulted in Osteoporosis. The consensus CPGs for these CIGs are shown in Fig. 3. State-achievement goals are shown in white; Action-enactment goals are shown in gray. Squares with dashed contour represent alternative actions available in the CIG that were not selected for the patient. Dots that appear before goals indicate additional hierarchy levels. Squares with bold lines in part (a) correspond to the PROforma CIG shown in Fig. 4.

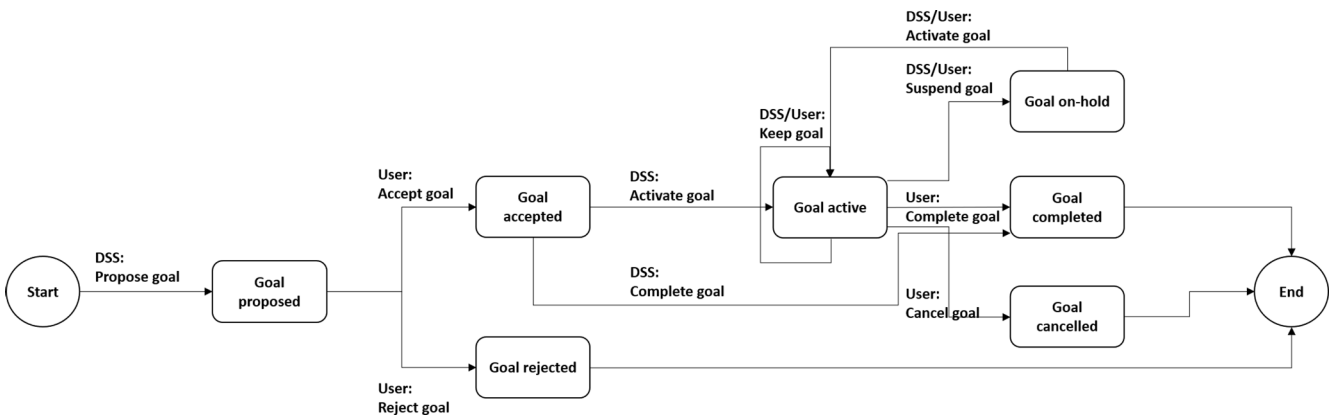


Fig. 7. The goal state chart with all states and state-transition events. Nodes represent states. Arcs represent state-transition events, which can be generated by clinician users or by GoCom.

Algorithm High-Level

```
1: ?new_problem = Retrieve_New_Problem(?patient)
2: ?patient_forest = Respond_To_New_Problem(?new_problem)
3: Check_Consistency_With_Subsumption(?patient_forest)
4: if (?consistent_start_medication_requests != []) then
5:     for ?consistent_MR in ?consistent_start_medication_requests do
6:         Respond_To_Non_Conflicted_MR(?consistent_start_medication_requests)
7:     end for
8: end if
9: while (?inconsistencies != []) do
10:    ?alternative_option_sets = Mitigate_Inconsistencies(?inconsistencies)
11:    ?explanations = Generate_Explanations(?alternative_option_sets)
12:    Display_To_User(?alternative_option_sets, ?explanations)
13:    Check_Consistency_With_Subsumption(?patient_forest)
14: end while
```

Fig. 8. High-level Pattern – top-level view of the Controller's algorithm.

Controller's algorithm then proceeds to address the next inconsistency. When all inconsistencies are dealt with, the algorithm checks the consistency of all the alternative forests and discards any forests that happen to have inconsistencies that might have occurred during the mitigation. Since the algorithm uses a strategy where goals can be discarded, it is impossible to reach a state where no solutions are found. For a pair of conflicting enactment goals, the algorithm, in effect, iterates through possible combinations of siblings that satisfy the parent goals until a non-conflicting pair is found.

Fig. 10 provides the pseudocode for generating alternative forests and Fig. 11 provides an illustration of three option sets (Fig. 11 b-d) derived from a conflicted tree (Fig. 11 a) for a set of three CIGs (Stroke, DU, Osteoporosis). Fig. 11d presents the "perfect" solution where no goals are canceled or rejected.

Consider the two conflicted actions in Fig. 11(a): start/stop PPI. During mitigation, a duplicate of the goal forest is made (See Line 6 in Pattern D), on which changes are implemented. For each conflicted action, its tree is retrieved and the parent goal is rerun in order to find siblings (Lines 7–11). The status of the conflicted action is set to "rejected" (if the status was "proposed") or "cancelled" (if the status was "active") (Lines 12–15). If an appropriate sibling action that is not inconsistent with the other goal in the inconsistency and that satisfies the same goal is found, the sibling replaces the inconsistent action (Line 17–20, 31–32); thus the active action is cancelled and the new sibling action(s) is proposed. For example, in the Stroke guideline (Fig. 11a), Aspirin has two replacement siblings (Clopidogrel and the combination of Aspirin + Dipyridamole). However, the actions start/stop PPI have no such siblings. In that case, two duplicate forests (Fig. 11 (b-c)) are created where in each, one of the conflicted actions and their parent goals are cancelled (in Fig. 11b "stop PPI" is rejected and the secondary prevention of Osteoporosis due to PPI is canceled; in Fig. 11c, "start PPI" is canceled and the secondary prevention of DU due to NSAID is canceled).

In addition, a third forest (Fig. 11d) is generated if the conflicted start-medication action was proposed and accepted **to counteract** the (adverse) effect of another medication. The Controller' algorithm searches for the "to counteract" connector term in all the goals that are involved in an inconsistency (See bottom of Fig. 11d). If the "to counteract" term is found, the goal where the term was found and the goal where the medication that is to be counteracted originated, are placed in a new inconsistency that is later mitigated, thus creating another alternative forest (Lines 25–28). In the illustrating example, start PPI in the DU guideline counteracts the effect of Aspirin that was started by the Stroke guideline. When the osteoporosis guideline suggests stopping PPI and the "start PPI to-counteract Aspirin" of the DU guideline is conflicted, the third forest is created while looking for sibling actions of the first medication that needed counteraction (Aspirin); a non-conflicted sibling (Clopidogrel) is proposed to replace the first, which

Algorithm 1 Pattern B

```
1: ?inconsistencies = []
2: for ?tree1 in ?forest do
3:     for ?tree2 in ?forest do
4:         for ?goal1 in ?tree1 do
5:             for ?goal2 in ?tree2 do
   ▷ consider two leaf goals(actions)
6:                 if (goal1.children == [] and goal2.children == []) then
7:                     if (Pattern_C_Inconsistency(?goal1, ?goal2) == true) then
   ▷ The inconsistency is created and saved in a temporary data structure for mitigation.
8:                         ?inconsistency = Save_Inconsistency(?goal1, ?goal2, ?forest)
9:                         ?inconsistencies ← Add_Inconsistency(?inconsistency)
10:                    end if
11:                end if
12:            end for
13:        end for
14:    end for
15: end for
16: function Pattern_C_Inconsistency(?goal1, ?goal2)
17:     if (Is_Equal_or_Subsumed(?goal1.Get_Object_Name(), ?goal2.Get_Object_Name())
18:         and (Is_Inconsistent(?goal1.Get_Object_Verb(), ?goal2.Get_Object_Verb()) then
19:             return true
20:     else
21:         return false
22:     end if
23: end function
```

Fig. 9. Pattern B (includes Pattern C) – Checking consistency of the forest while checking for subsumption.

in turn is cancelled. Since the PPI that was started to counteract the effect of the first medication is no longer needed, it is thus completed, along with its parent goal. **Counteraction dependencies** are specified in the CIGs (see Section 3.1.1.2) and are inserted into the corresponding Goal Tree (e.g., PPI in the DU guideline is a counteraction to Aspirin).

At the end of the mitigation, each goal is assigned with a life cycle status. Each parent goal-node assumes its status according to the status of its children. If all the children are discarded/cancelled, the parent is discarded/cancelled, if at least one child is active, the parent is active. This is however not shown to the clinician, as only the leaf goals have explanations and a recommended action.

The alternatives resulting from the mitigation (Line 32) represent the aggregated alternative option sets that provide the clinician with all possible combinations of the patient's management plans for the different goals, from which the clinicians can choose the option they consider to be the best.

Currently, the Controller detects inconsistencies between Action-enactment goals (e.g., start medication vs. stop medication) and inconsistencies between a pair of Physiological Effect State-achievement goals. However, mitigation is currently performed only for Action-enactment goals.

3.2.4. Explanation strategy

To gain clinician trust and resilience, decision support systems should be able to explain their recommendations [53]. GoCom relies on the aggregated alternative goal forests that contain the mitigated solutions to derive its explanation. It uses three strategies for dynamically constructing the explanations for multimorbidity patients.

First, for each option set, the controller generates a high-level explanation that summarizes it. The high-level explanation describes how many (and which) goals were met (kept or completed) or cancelled, and the actions that will be done if the option set is chosen. Lines 7–12 as well as line 33 in Pattern F (Fig. 12) describe how the high-level explanation is generated automatically, through counting the number of met and unmet goals and adding to the explanation the required actions of the option set. Fig. 13 shows an example output table of a patient that had Stroke and DU and was diagnosed with Osteoporosis due to PPI.

Second, to allow the clinician users to understand why an action is needed, the goal hierarchy leading to the recommendation is also shown. For example, for the high-level goal "secondary prevention of stroke", a lower-level Physiological Effect goal of Decreased Platelet Aggregation is proposed, and for it the following action-enactment goals are placed into context: Keep Aspirin or Replace Aspirin with Clopidogrel. Column 1 of Fig. 13 shows the goal hierarchy for three goals taken from the three guidelines.

Third, GoCom automatically generates explanations for each Action-enactment goal (the different cells shown in Fig. 13), according to the cases presented in Table 2. Table 2 considers different combinations of a verb and a goal state-transition in each row, describes the algorithmic state of that combination, and specifies whether the explanation is taken directly from the clinical guideline or is generated by the Controller's algorithm. The last column presents examples for explanations for each case.

Basing the recommendations of GoCom directly on a single evidence-based guideline recommendation is the simplest case (See Row 1.1 in Table 2). This strategy is used for leaf nodes that propose starting a new medication (see Fig. 11d – start Clopidogrel) or keeping active ones (see Fig. 11b – keep PPI). In those simple cases, the clinical guideline must contain a recommendation that indicates this medication as a valid option. Hence, in addition to other metaproperties, Action-enactment

Algorithm 1 Pattern D

```
?alternative_option_sets = []
while ?inconsistencies! = [] do
    function Mitigate_Inconsistency(?inconsistency)
        for ?goal in ?inconsistency do
            ?new_inconsistency_flag = false
▷ duplicate current patient forest and make changes in the duplicate
            ?duplicated_forest = Duplicate_Forest(?forest)
            ?duplicated_goal =?duplicated_forest.Get_Duplicated_Goal(?goal)
            ?guideline =?duplicated_goal.Get_Guideline()
            ?patient =?duplicated_goal.Get_Patient()
            ?parent_goal =?duplicated_goal.Get_Parent()
            ?sibling = Rerun(?guideline, ?patient)
            if (?duplicated_goal.status == "Proposed") then
                Update_Goal_Status(?duplicated_goal, "Rejected")
            else if (?duplicated_goal.status == "Active") then
                Update_Goal_Status(?duplicated_goal, "Cancelled")
            end if
▷ add sibling if found and reject or cancel current action enactment goal. Currently considering only a case of one sibling
            if (?sibling! = null) then
                ?other_inconsistent_goal =?inconsistency.Get_Other_Inconsistent_Goal()
                ?parent_goal.addChild(?sibling)
                Update_Goal_Status(?sibling, "Proposed")
                if (Pattern_C_Inconsistency(?sibling, ?other_inconsistent_goal) == true) then
                    ?new_inconsistency = Save_Inconsistency(?sibling, ?other_inconsistent_goal, ?duplicated_forest)
                    ?inconsistencies ← Add_Inconsistency(?new_inconsistency)
                    ?new_inconsistency_flag = true
▷ if the action-enactment goal was accepted to counteract the effects of another medication,run mitigation to try and find a replacement for the medication that needs to be counteracted.
                else if (?goal.Get_Connector_Term() == "to_counteract") then
                    ?counteract_goal =?goal.Get_Counteract_Goal()
                    ?new_inconsistency = Create_New_Inconsistency(?goal, ?counteract_goal, ?duplicated_forest)
                    ?new_inconsistency_flag = true
                end if
            end if
            if ?new_inconsistency_flag == false then
                ?alternative_option_sets ← Add_Alternative_Forest(?duplicated_forest)
            end if
        end for
    end function
end while
```

Fig. 10. Pattern D (includes Pattern E): Inconsistency mitigation via aggregation.

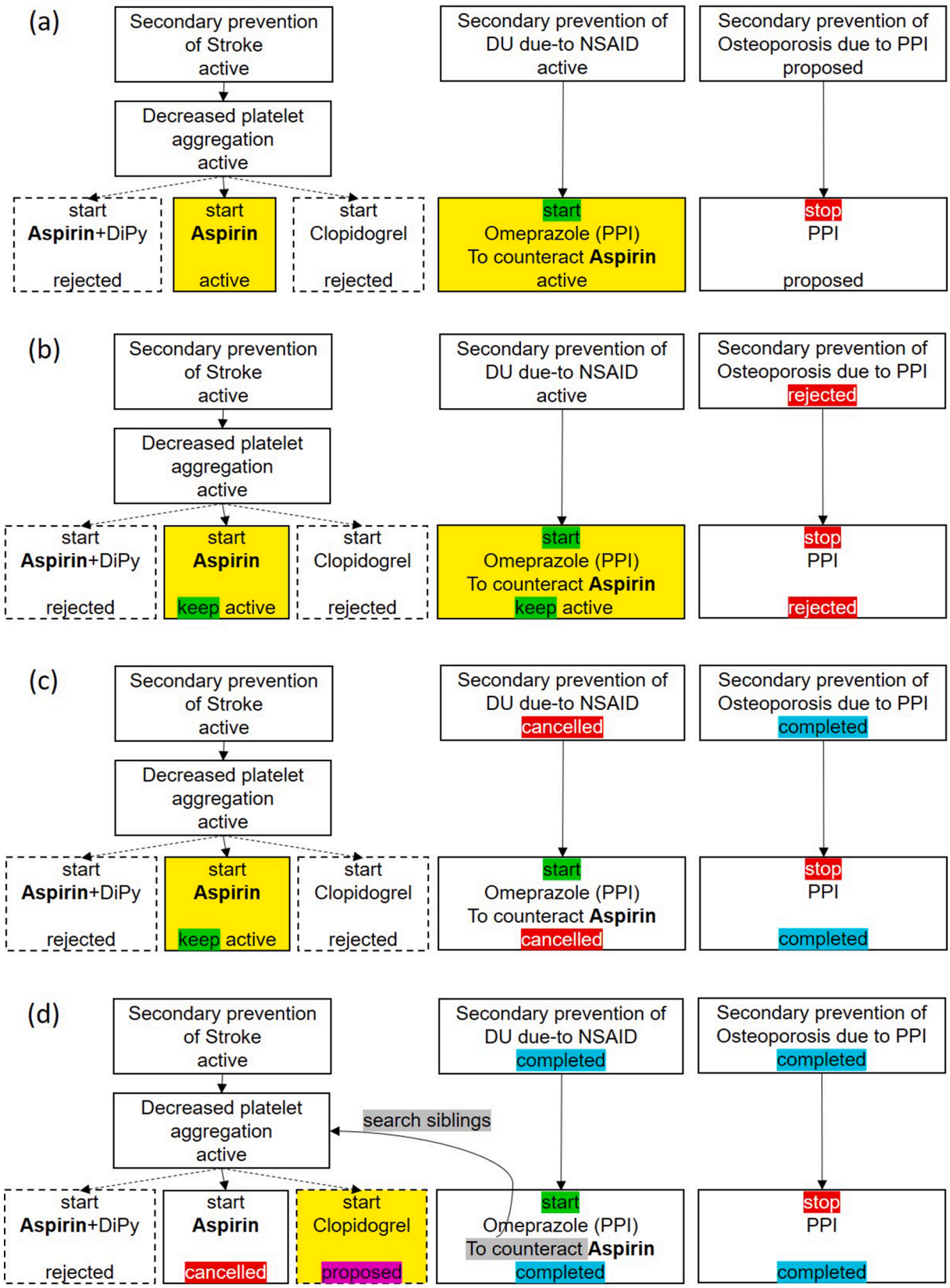


Fig. 11. Aggregated mitigation strategy explained. (a) conflicted goal forest for a patient who is taking Aspirin for secondary prevention of stroke, PPI for secondary prevention of DU due-to Aspirin, who has Osteoporosis due-to PPI and a proposed action to stop the PPI for secondary prevention of Osteoporosis. Current medication and medications suggested in an alternative option sets are shown in yellow. Conflicted actions are show in green and red. (b-d) alternative goal forests that present alternative option sets.

Algorithm Pattern F

```
for ?alternative_forest in ?alternatives do
    ?high_level_explanation = null
    ?count_goals_met = 0
    ?count_goals_not_met = 0
    for ?tree in ?alternative_forest do
        for ?goal in ?tree do
▷ counting goal state transition (met or not met) and adding the required
actions for the high-level explanation
            if ?goal.Get_State_Transition() == "Accept"
                or ?goal.Get_State_Transition() == "Keep"
                or ?goal.Get_State_Transition() == "Complete"
                or ?goal.Get_State_Transition() == "Activate"  then
                ?count_goals_met ++;
            else if ?goal.Get_State_Transition() == "Reject"
                or ?goal.Get_State_Transition() == "Cancel"
                or ?goal.Get_State_Transition() == "Suspend" then
                ?count_goals_not_met ++;
            end if
            ?high_level_explanation.Add_Goal_Verb_And_Object
                (?goal.Get_Verb(), ?goal.Get_Object())
▷ consider leaf nodes
            if ?goal.Get_Children == []) then
▷ generate explanation as detailed in Table 2
                ?explanation = Generate_Explanation_For_Goal(?goal)
                Set_Explanation(?goal, ?explanation)
▷ single child goal
                if (?goal.Get_Parent().Get_Number_Of_Children == 1) then
                    ?goal_action = Get_Goal_Verb_And_Object(?goal)
                    Display_Goal_And_Explanation(?goal_action, ?goal.getExplanation())
▷ replacement goal
                else if (?goal.Get_Parent().Get_Number_Of_Children > 1
                    and ?goal.Get_Parent().Get_Explanation_Type() == "replace" then
                    conflicted_action = goal.Get_Parent().Get_Inactive_Child()
                    ?sibling = goal.Get_Parent().Get_Active_Child()
                    ?goal_action = "Replace"?conflicted_action"with"?sibling
                    Display_Goal_And_Explanation(?goal_action, ?sibling.Get_Explanation())
▷ multiple children goal
                else if (?goal.Get_Parent().Get_Number_Of_Children > 1
                    and ?goal.Get_Parent().Get_Explanation_Type() == "multiple" then
                    for child_goal in ?goal.Get_Parent().Get_Children() do
                        Display_Goal_And_Explanation(?child_goal, ?child_goal.Get_Explanation())
                    end for
                end if
            end if
        end for
    end for
    Display_High_Level_Explanation
        (?high_level_explanation, ?count_goals_met, ?count_goals_not_met)
end for
```

Fig. 12. Pattern F Explanation strategy.

	Option set 1	Option set 2	Option set 3
High-level explanation	All goals are met (kept/completed). The actions are: replace Aspirin with Clopidogrel and stop PPI.	One of the goals is discarded. The goal Secondary prevention of Stroke via antiplatelet is satisfied, the goal Secondary prevention of Osteoporosis-due-to-PPI is satisfied and the goal Secondary prevention of DU-due-to-NSAID is unsatisfied. The actions are: keep aspirin and stop PPI.	One of the goals is discarded. The goal Secondary prevention of Stroke via antiplatelet is satisfied, the goal Secondary prevention of DU-due-to-NSAID is satisfied and the goal Secondary prevention of Osteoporosis-due-to-PPI is unsatisfied. The actions are: keep aspirin and keep PPI.
G1.6.1 Secondary prevention of Stroke. Decreased platelet aggregation	1 1.1 Action: Replace Aspirin with Clopidogrel Goal active Explanation: p. 2198: 3. Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (Class IIa; Level of Evidence B). This recommendation also applies to patients who are allergic to aspirin. Grade: B	2 1.1 Action: Keep Aspirin Goal active Explanation: p. 2198: 2. Aspirin (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. Grade: A	3 1.1 Action: Keep Aspirin Goal active Explanation: p. 2198: 2. Aspirin (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. Grade: A
G2.5 Secondary prevention of Duodenal Ulcer .Secondary prevention of Duodenal Ulcer due to NSAID	4 1.4 Action: start PPI Goal completed Explanation: PPI was provided to counteract the effects of Aspirin. If Aspirin is no longer needed then the goal Secondary prevention of DU-due-to-NSAID is completed, and PPI is stopped. Grade: (auto generated)	5 1.6 Action: start PPI Goal cancelled Explanation: There has been an indication to stop PPI due to an interaction. Since PPI is the only option recommended for the goal Secondary prevention of DU-due-to NSAID, the goal is cancelled. Grade: (auto generated)	6 1.1 Action: Keep PPI Goal active Explanation: When DU develops and aspirin is maintained, PPI should be added to prevent ulcer bleeding. 28. Aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1 – 3 days and certainly within 7 days. Long-term daily PPI therapy should also be provided. Grade: A
G3.2.1 Secondary prevention of Osteoporosis .Secondary prevention of Osteoporosis-due-to-PPI	7 2.1 Action: Stop PPI Goal completed Explanation: If the recommendation to stop PPI is accepted, then the goal of Secondary prevention of Osteoporosis-due-to-PPI is completed. Grade: (auto generated)	8 2.1 Action: Stop PPI Goal completed Explanation: If the recommendation to stop PPI is accepted, then the goal of Secondary prevention of Osteoporosis-due-to-PPI is completed. Grade: (auto generated)	9 2.2 Action: Stop PPI Goal rejected Explanation: There has been an indication to reject stop PPI due to an interaction with start PPI (with no sibling alternative in the Osteoporosis guideline). Therefore in this option set we keep the PPI and reject the goal Secondary prevention of Osteoporosis-due-to-PPI. Grade: (auto generated)

Fig. 13. Goal-based aggregated explanations generated for three decision options that address (satisfy or discard) three clinical goals: (a) secondary prevention of stroke via antiplatelet therapy that decreases platelet aggregation, (b) secondary prevention of DU due to NSAID, (c) prevention of secondary osteoporosis due to PPI. The high-level explanation in the first row provides a brief summary of the option set, detailing the number of goals that are met and the number of goals discarded, as well as the leaf action-enactment goals recommended. Each cell in the output table has a number – number with yellow background refers to the number of the cell. Numbers with blue background refer to the type of explanation that was generated according to the lines in Table 2.

goals contain the textual recommendations from the guideline and their grade of evidence, which are presented to the clinician along with the proposed action. In Fig. 13 the cells marked with 1.1 provide the default explanation from the guideline.

More complex cases require parametric auto-generated explanations. The parameters are bound with values corresponding to the goals that are addressed (including Action-enactment goals). In Table 2 (last column), the parameter values are underlined and the rest of the textual explanation is constant for each explanation type. There are seven kinds of auto-generated explanations, which depend on the combination of verb and state transition. Table 2 includes only explanations shown to clinician users; for some combinations of verbs and state transitions GoCom proceeds without consultation with the clinician. These cases include (a) the "propose" state transition that is used by GoCom to generate a new goal. The explanation is not presented before the inconsistencies between goals are checked and alternative goal trees are generated. The Controller's mitigation algorithm simulates decisions made by clinicians to accept or reject a proposed goal. Alternative explanations are provided for these two options (Table 2 rows 1.1 and 1.2); (b) the life-cycle of medication (or procedure) requests focuses on supplies of material entities such as medications supplied to a patient. Stopping a medication is reflected in the life-cycle as a transition of the material entity into a state of non-existence. Therefore, a '**stop** medication (procedure)' goal can either be accepted, then it immediately transitions into 'completed' or it can be rejected. It does not go through the transitions of keep, suspend, activate, cancel. If a medication was completed or rejected, it needs to be proposed again in order to start its new life cycle.

Pattern F (Fig. 12, lines 16–27) considers the number of children that the parent goal has for generating the explanations based on the third

Table 2
Explanation generation according to the relevant goal life cycle.

	State-transition	verb	Algorithmic case	Explanation type	Example
1.1	Accept / Keep	start	The Controller suggests to accept/keep a goal that has been proposed and provides the recommendation from the guideline	Default guideline explanation	Action: start Aspirin Goal accepted Explanation: p. 2198: 2. Aspirin (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. Grade: A
1.2	Reject/ Suspend		The Controller suggests to reject/suspend a goal that has been proposed and has no alternative sibling actions	Auto-generated explanation	Action: start PPI Goal rejected There has been an indication to **reject/suspend** PPI due to an inconsistency. Since PPI is the only option recommended for the goal Secondary prevention of DU-due-to NSAID, the goal is rejected. Grade: (auto generated)
1.3	Activate		The Controller suggests to activate a goal that has been on-hold	Auto-generated explanation + Default guideline explanation	Action: start Aspirin Goal activated Explanation: There has been an indication that Aspirin should be activated after suspension, as a treatment for goal Decrease Platelet Aggregation in the Stroke guideline. p. 2198: 2. Aspirin (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. Grade: A, (auto generated)
1.4	Complete		The Controller suggests to complete a goal that has been active but is no longer needed	Auto-generated explanation	Action: start PPI Goal completed PPI was provided to counteract the effects of Aspirin. If Aspirin is no longer needed then the goal Secondary prevention of DU-due-to-NSAID is completed, and PPI is stopped. Grade: (auto generated)
1.5			The Controller suggests to complete a goal that has been active and is now achieved	Auto-generated explanation	Action: start PPI for two weeks Goal completed PPI was prescribed for Two weeks. The goal is now achieved. Since PPI is the only option recommended for the goal Secondary prevention of DU-due-to NSAID, the goal is completed, and PPI is stopped. Grade: (auto generated)
1.6	Cancel		The Controller suggests to cancel a goal that has been active, has an inconsistency, and has no alternative sibling actions	Auto-generated explanation	Action: start PPI Goal cancelled There has been an indication to **stop** PPI due to an inconsistency. Since PPI is the only option recommended for the goal Secondary prevention of DU-due-to NSAID, the goal is cancelled. Grade: (auto generated)
2.1	Accept/ Complete	stop	The Controller suggests to accept stopping an active goal (see 1.6). If the clinician accepts then the goal is completed	Auto-generated explanation	Action: stop PPI Goal completed If the recommendation to **stop** PPI is accepted, then the goal of Secondary prevention of Osteoporosis-due-to-PPI is completed. Grade: (auto generated)
2.2	Reject		The Controller suggests to reject a goal of stopping an action, that has been proposed, is involved in an inconsistency, and has no alternative sibling actions	Auto-generated explanation	Action: stop PPI Goal rejected There has been an indication to **reject** stop PPI due to an inconsistency with start PPI (with no sibling alternative in the Osteoporosis guideline) Therefore in this option set we keep the PPI and **reject** the goal Secondary prevention of Osteoporosis-due-to-PPI. Grade: (auto generated)

strategy described above. If the parent goal has one child (Lines 16–18), the explanation is generated according to Table 2. If the parent goal has two children (Lines 19–24) where child1 is cancelled and child2 is proposed, the explanation has the title "replace child1 with child2" and shows the recommendation from the guideline for child2 (the replacement). If the parent goal has multiple proposed children (Lines 25–27), the explanation is comprised of the individual explanations for each action-enactment goal, according to Table 2.

3.3. View

The View presents the clinician with all the available patient data and allows the clinician to view it while receiving decision support for selecting management plans when a new clinical goal is introduced.

An example screenshot can be seen in Fig. 14. Among the patient information that is provided to the clinician, are patient demographics and anthropomorphics (including name, age, height, weight and BMI – see top row), the patient Visit Log that provides the visit notes from previous patient visits (top right), and Investigations (patient observations - bottom right) that include laboratory test results and results of

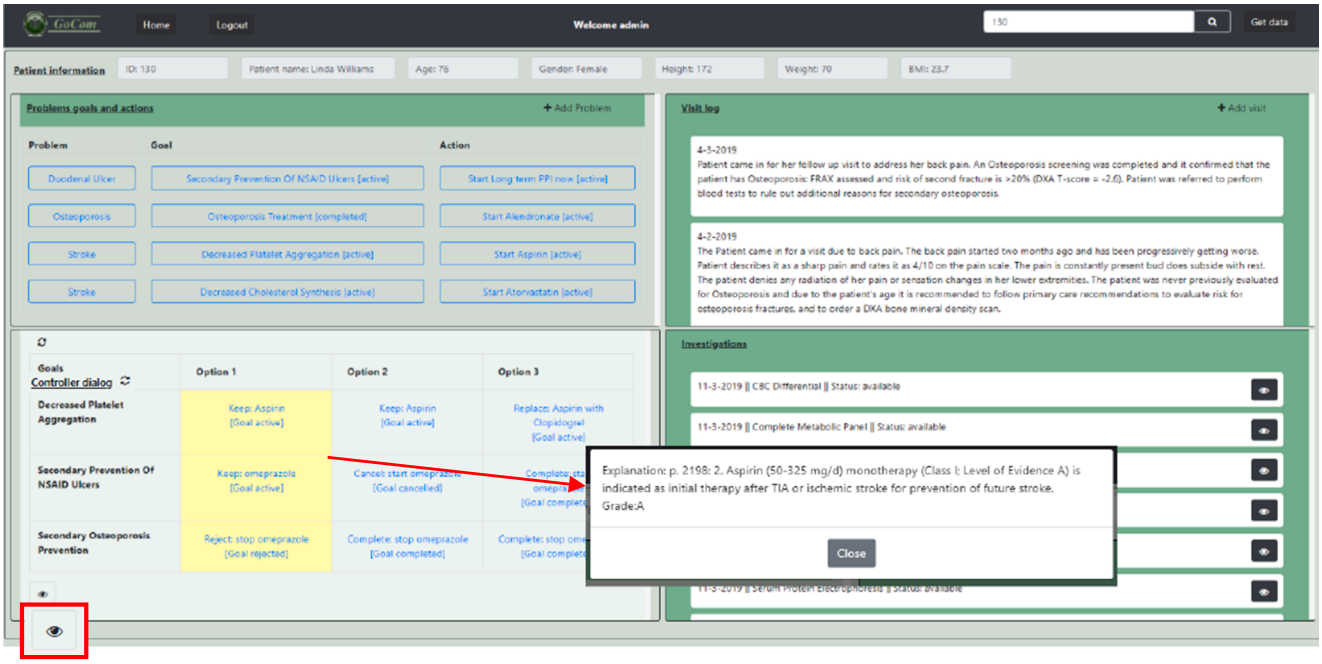


Fig. 14. A screenshot showing an example of the user interface produced by GoCom for a patient with three morbidities. The insert shows an explanation for the goal Decreased Platelet Aggregation for one of the option sets (Option 1). Under the Controller dialog table, there is an option to zoom in and view the table in full screen.

various procedures. The clinician may scroll through the visit log and zoom into the investigations screen.

Unique to our approach is the left part of the user interface screen. The top part presents a table showing the current problems, respective clinical goals, and the active actions (leaf Action-enactment goals) satisfying the goals. When mitigation is required, the Controller's dialog (bottom left) displays the explanations for the different option sets in a table, based on the aggregated decision-option sets. Clicking on the table cells opens a window that displays the complete explanation for a goal of the decision option set – see insert of Fig. 14. Clicking on the "eye" symbol on the bottom left of the screen of Fig. 14 displays the complete explanation table as shown in Fig. 13.

The View is implemented using the Spring framework [54], which is well suited for implementation of the Model-View-Controller architecture. The interface is web-based and hosted on an online Heroku server [54]. The interface is not currently linked to a hospital system but instead draws its patient data from tables serving as an EHR, as described in Section 3.1.4.1.

4. Methods for the evaluation of GoCom's Controller's functionality and usefulness

We carried out an evaluation of GoCom's functionality and usefulness by applying it to six case study examples of complex patient scenarios, each involving multimorbidity and different types of recommendation inconsistencies. The knowledge acquisition process for generating the case study examples was our modification [47] of the Consensus Method by Shalom et al. [46] (see Section 3.1.2).

The clinicians (coauthors IH, RA, NK) and informaticians (coauthors MP, AK, SWT) discussed examples of inconsistencies between guideline recommendations for complex multimorbidity patients, addressing among other themes, adverse events and their effects on medication choice, as well as patient preferences. The clinicians defined clinical scenarios for which they selected portions from relevant and up-to-date clinical guidelines. The guidelines used for the case studies were secondary prevention of cardiovascular disease (CVD)[55], management of patients with duodenal ulcer bleeding (DU) [56], prevention and management of Hypertension [57], management of Hereditary Angioedema [58], Stroke Prevention in Patients with Stroke and TIA [41], Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis [48], Standards of care in Diabetes [59], Clinical Practice Guideline for the Management of Candidiasis [60], Practice guideline for the treatment of patients with schizophrenia [61], and the American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis [62].

For each scenario, the clinicians also produced realistic data sets—consisting of diagnoses, visit summaries, laboratory test results and active medications—and defined gold standard management plans consisting of all alternative therapy options for each case study, including their justification.

Table 3 provides a high-level description of the six case studies As an example, Appendix A shows the descriptions for one case (Hypertension and Hereditary Angioedema) along with the gold standard solutions. All patient records were manually added to the patient model using PostgreSQL.

Below we describe the methods for functional evaluation and usability in an experiment where GoCom was used to support patient management by senior medical students. The evaluation results are provided in Section 5.

4.1. Methods for evaluation of system functionality

The functionality of the GoCom system was developed while studying the combination of the CVD ,DU and Osteoporosis guidelines and was evaluated by testing the output of the Controller for the six case studies against the defined gold standard. The system produced results matching the gold standard solutions (See Appendix A for the gold standard of Case #1). The system recommendations for the most complicated case (Case #3) that has three comorbidities (Stroke, DU, Osteoporosis), considers the subsumption hierarchy (of Aspirin is-a NSAID), considers medications given to counteract the effects of other medications (omeprazole to counteract aspirin) and produces aggregated options sets is shown in Figs. 13 and 14.

Table 3
High-level description of the six case studies used for evaluation.

	Guidelines involved	Brief description of the case study	Goals and active medications for the patient at the start of the case study (medication in bold)	Existing inconsistencies and unmet goals	Number of decisions (#options per recommendation); Total #recommendations	Data set description
Case 1	-Hypertension, -Hereditary Angioedema	A 38-year old male was prescribed Lisinopril (ACE Inhibitor) for Hypertension. Three months later, the patient came in with symptoms of Angioedema that was eventually diagnosed as Recurrent Angioedema due to ACEI. The treatments included replacing Lisinopril with a medication from the ARB or CCB or Thiazide Diuretics family, and prescribing medication for treatment of Hereditary Angioedema as well as preventative management and blood pressure monitoring.	a) Diagnose cause of Angioedema (Recurrent Angioedema due to ACEI): goal proposed b) Acute Treatment of Hereditary Angioedema (**start C1 esterase inhibitor, Start Ecallantide, Start Icatibant**): goal proposed c) Self-treatment of Future Acute Attacks of Hereditary Angioedema (**start C1 esterase inhibitor emergency kit) :** goal proposed d) Preventative management of Hereditary Angioedema (**Stop ACEI**): goal proposed **e)** Treatment of Hypertension. Decreased_Blood_Pressure (**start ACEI**): goal active	1) Unmet goals: all 5 goals are not met at the start of the scenario, except for goal e. But it becomes unmet when ACEI is stopped. 3 alternatives are suggested to the ACEI. 2) Side effect: Hereditary Angioedema suspected: due-to ACEI 3) Conflicting actions: start/stop ACEI	In the pilot study: 6 decisions (1, 3, 1, 1, 3, 1) In the evaluation experiment: 3 option sets addressing the conflicted goal and its alternatives, as well as all the other recommendations 10 recommendations See Appendix A	- Age, gender, height, weight, BMI - S/P STEMI 10 years ago - Basic Metabolic panel - CBC with differential - Complement protein 4 (C4) level - C1 inhibitor level − 5 visit notes from past 3 months
Case 2	-CVD secondary prevention -DU diagnosis, treatment, and prevention	A 68 year-old male that was treated for secondary prevention of cardiovascular disease and developed Duodenal Ulcer as a result of taking Aspirin. The treatment recommendation included replacing Aspirin with Clopidogrel and starting long-term PPI for secondary prevention of Duodenal Ulcer.	a) Diagnose cause of DU (DU due to NSAIDs) : goal proposed b) CVD secondary prevention. Decreased_Platelet_ Aggregation (**start Aspirin**): goal suspended c) CVD secondary prevention. Decreased_ Cholesterol_Synthesis (**start Atorvastatin**) : goal active d) Treatment of DU due-to NSAID (**Stop Aspirin)** + .Inhibition_Gastric_Acid_ Secretion .(**start PPI short-term**): goal completed **e)** Secondary prevention of DU due-to NSAID. Inhibition_Gastric_Acid_Secretion. (**start PPI long-term**) : goal proposed	1) Unmet goals: goals a, b, e unmet. Clopidogrel is suggested as an alternative to Aspirin. 2) Side effect: DU: due-to Aspirin	In the pilot study: 4 decisions (1, 2, 1, 1) In the evaluation experiment: 2 option sets addressing the conflicted goal, its alternative and the other recommendations 5 recommendations 6 after update of gold standard	- Age, gender, height, weight, BMI -Gastroscopy summary -Basic metabolic panel -CBC with differential -Coagulation panel -Liver function tests **Results pending -H. Pylori -Ulcer biopsy − 5 visit notes from past 10 years
Case 3	-Stroke secondary prevention -DU-due-to NSAID secondary prevention -Osteoporosis due-to PPI secondary prevention	A 76 year-old female who had a Transient Ischemic Attack, took Aspirin for secondary prevention of Stroke, then developed Duodenal Ulcer due to the Aspirin. The Aspirin was stopped for a few days and the patient was prescribed PPI for treating the DU. As a consequence, the ulcer healed. Aspirin was resumed for secondary prevention of Stroke while continuing the PPI long-term, for secondary prevention of DU due to Aspirin. 9 years later, the patient has developed osteoporosis, to which PPI is a contributing factor.	a) Secondary prevention of Stroke. Decreased_Platelet_Aggregation (**start Aspirin**) : goal active b) Secondary prevention of DU_due-to_NSAID. Inhibition_Gastric_Acid_Secretion (**start PPI long-term**) : goal active c) Stroke.Decreased_ Cholesterol_Synthesis (**start Atorvastatin**) : goal active d) Treatment of Osteoporosis. Bone_Resorption_ Inhibition (**start Bisphosphonates) : goal active** e) Secondary prevention of Osteoporosis due-to PPI (**stop PPI**): goal proposed	1) Unmet goals: e While running the Controller, additional goals become unmet for different solution sets: a, b. Clopidogrel is suggested as an alternative to Aspirin and it is suggested to complete the PPI treatment. 2) Side effects: DU: due-to Aspirin Osteoporosis: due-to PPI 3) Conflicting actions: start/stop PPI	3 option sets, each addressing the 3 inconsistent goals 7 recommendations See Figs. 13, 14 8 after update of gold standard	Age, gender, height, weight, BMI FRAX, DXA bone mineral density (BMD) Thyroid panel, Serum Protein electrophoresis, PTH, Vitamin D, 24hr urine collection, Complete metabolic panel, CBC differential, Celiac disease antibodies. 6 physician visit notes over the past 14 years.
Case 4	-Diabetes -Recurrent fungal infections	A 57 year-old female had a Transient Ischemic Attack in 2010. In 2018, patient was diagnosed with Diabetes and prescribed	a) Cardiovascular disease secondary prevention.Decreased Platelet Aggregation (**start Aspirin**) : goal active b) Cardiovascular disease secondary prevention.Decreased Cholesterol	a) Unmet goals: e, f, g ,h. Goal d becomes unmet when running the controller. Liraglutide is suggested as an alternative to	2 option sets, each addressing the inconsistent and unmet goals. 10 recommendations	Age, gender, height, weight, BMI, as well as multiple instances of: Comprehensive Metabolic Panel (CMP), Complete

(*continued on next page*)

Table 3 (*continued*)

	Guidelines involved	Brief description of the case study	Goals and active medications for the patient at the start of the case study (medication in bold)	Existing inconsistencies and unmet goals	Number of decisions (#options per recommendation); Total #recommendations	Data set description
		Metformin. However, Metformin was not enough to control her Diabetes and she was put on dual therapy with Liraglutide (GLP1RA). The patient later complained about injections (Liraglutide) and Liraglutide was switched to Empagliflozin (SGLT2). Shortly after starting Empagliflozin, the patient started having recurrent fungal infections (Candidiasis), to which SGLT2 is a contributing factor. GLP1RA and SGLT2 are the best choices for patients with cardiovascular disease.	Synthesis (**start Atorvastatin**) : goal active c) Pharmacological Dual Therapy. Decreased Gluconeogenesis (**start Metformin**) : goal active d) Pharmacological Dual Therapy. Established ASCVD (**start Empagliflozin**) : goal active e) Diagnose cause of RFI (Recurrent Vulvovaginal Candidiasis due to SGLT2) : goal proposed f) Treatment of Recurrent Vulvovaginal Candidiasis (**start Fluconazole short term**)) : goal proposed g) Prevention of Vulvovaginal Candidiasis (**start Fluconazole long term**)) : goal proposed h) Long Term Prevention of Vulvovaginal Candidiasis (**stop Empagliflozin**)) : goal proposed	Empagliflozin. Long term Fluconazole will not be given if Empagliflozin is replaced. b) Side effects: Vulvovaginal Candidiasis due to SGLT2 c) Conflicting actions: start/stop Empagliflozin		Blood Count panel (CBC), Lipid panel, HBA1C, Vaginal sample workup. 8 physician visit notes over the past 10 years.
Case 5	-Schizophrenia -Diabetes	The patient is a 45 year-old female. In 2012 the patient was diagnosed with Schizophrenia. After trying out a number of medications, her schizophrenia is controlled with Olanzapine, which she must continue to take even though she gained a significant amount of weight as a side effect of Olanzapine. 6 years later, the patient is diagnosed with Diabetes. Since the patient experienced gastrointestinal side effects with Metformin, and due to cost issues, the patient is prescribed Glimepiride (Sulfonylurea), with which her Diabetes is now well controlled. The patient however experiences additional weight gain due to the new Sulfonylurea medication, despite adhering to a strict diet.	a) Schizophrenia.Long-term treatment of Schizophrenia (**start Olanzapine**) : goal active b) Diabetes. Pharmacological Monotherapy-Decreased Glycemia (**start Glimepiride**) : goal active c) Diagnose cause of Weight Gain (weight gain due to Sulfonylurea) : goal proposed d) Treatment of Schizophrenia. Monitoring and Prevention of Weight Gain : goal active	1.Unmet goals: Goal c is unmet. B becomes unmet when the Controller is run. Liraglutide is suggested as a replacement for Glimepiride. Aripiprazole is suggested as a replacement for Olanzapine. If Olanzapine is replaced, weight monitoring due to Olanzapine is completed. 2.Side effects: Weight gain due to Sulfonylurea. 3.Conflicting actions: Start/stop Glimepiride.	3 option sets addressing the conflicted goal, as well as alternatives for the different medications causing the problem. 7 recommendations 8 after update of gold standard	Age, gender, height, weight, BMI, as well as multiple instances of: Comprehensive Metabolic Panel (CMP), Complete Blood Count panel (CBC), Lipid panel, HBA1C. 7 physician visit notes over the past 8 years.
Case 6	-Diabetes -Hyperthyroidism -Hypertension	The patient is a 38 year-old female. Patient is diagnosed with Diabetes and Hypertension in 2014 and is prescribed Metformin and Atorvastatin and Lisinopril. Her Diabetes is well controlled. In 2016 the patient is diagnosed with hyperthyroidism and is treated with methimazole. During the latest visit the	a) Pharmacological Monotherapy-Decreased Gluconeogenesis (**start Metformin**) : goal active b) Hypertension. Decreased_Blood_Pressure (start Lisinopril) : goal active c)Diabetes. Dyslipidemia Treatment-Decreased Cholesterol Synthesis(**start Atorvastatin**) : goal active d) Hyperthyroidism Treatment-Decreased Thyroid Hormone Iodination(**start Methimazole**) : goal active e) Diabetes Preconception-Counseling-Management of Pharmacological Treatments (counseling for	1.Unmet goals: e, f ,g ,h i. Goals a, b, c and d become unmet when the Controller is run. Insulin is suggested as a replacement for metformin. Nifedipine is suggested as a replacement for Lisinopril. It is suggested that Atorvastatin should be stopped. Propylthiouracil is suggested as a	2 option sets addressing the medication replacements for preconception care. 13 recommendations	Age, gender, height, weight, BMI, as well as multiple instances of: Comprehensive Metabolic Panel (CMP), Complete Blood Count panel (CBC), Lipid panel, HBA1C, Urine Biochemistry, RAIU Scan, Thyroid Panel, TSI. 8 physician visit notes over the past 6 years

(*continued on next page*)

Table 3 (*continued*)

Guidelines involved	Brief description of the case study	Goals and active medications for the patient at the start of the case study (medication in bold)	Existing inconsistencies and unmet goals	Number of decisions (#options per recommendation); Total #recommendations	Data set description
	patient wants to discuss options for pregnancy. All of the medications she is using need to be managed / changed since they are teratogenic.	management of patient medications) : goal proposed f) Diabetes Preconception-Counseling (refer patient to eye exam) : goal proposed g) Diabetes Preconception-Care-Cellular Activity Alteration(**start Folic acid**) : goal proposed h) Diabetes Preconception-Care-Decreased Thyroid Hormone Secretion (**start Potassium iodide**) : goal proposed i) Diabetes Preconception-Counseling-Diet Management(refer patient to dietitian) : goal proposed	replacement for Methimazole. 2.Side effects: All current medications interact with pregnancy 3.conflicting actions: All current medications interact with pregnancy		

4.2. Methods for evaluation of system usefulness in two empirical studies

The ***usefulness*** of the approach in supporting clinicians was evaluated in two empirical studies: (1) in a preliminary experiment with ten senior medical students at the end of their sixth and final year from the Technion Medical School, who worked on two complex case studies with a total of 16 recommendations; (2) in a larger experiment with 27 senior medical students, who worked on six complex case studies with a total of 55 recommendations. We assessed the impact of the recommendations given by the GoCom system on completeness and correctness.

In both studies, the participating medical students have completed their courses, including rotations in general internal medicine, and were considered as junior clinicians. In the preliminary experiment, the students received the first two scenarios described in Table 3 and were asked to arrive at a diagnosis and to list all potential management option sets for each of the two scenarios. Each student worked on one case with GoCom and one case without it. In the second experiment, the students received four scenarios in addition to the first two.

Our hypothesis was one-sided: that the junior clinicians would perform better with GoCom. Performance was measured in terms of completeness and correctness, as defined by Shalom et al. in [63]. Accordingly, ***completeness*** is defined as the percentage of clinical diagnoses and clinical actions (e.g., medication prescriptions, ordering of laboratory tests, etc.) specified by a participant out of the total set of diagnoses and actions indicated by the clinical guidelines and specified in the gold standard.

Correctness is defined as the percentage of correct clinical diagnoses and clinical actions (e.g., medication prescriptions, ordering of laboratory tests, etc.) out of the entire set of diagnoses and actions specified by a participant.

We used the Wilcoxon Rank-sum test to evaluate these hypotheses.

Three clinicians (coauthors IH, RA and NK) prepared the gold standard solution for the case studies, considering the diagnoses and all indicated management options mentioned in clinical guideline recommendations. As in [63], it was agreed that if the participants identify additional potential management options, then the gold standard would be extended to include them as well. Table 3 provides details regarding the case studies used for both experiments. Appendix A provides as an example the full details of Case 1. The second to last column of Table 3 lists the total number of recommendations. Participants identified an option for Cases 2 and 3 (Prasugrel as an antiplatelet) and case 5 (Clozapine) that did not exist as part of the clinical guidelines, but was accepted by the clinicians as part of the gold standard. Because GoCom was based only on the clinical guidelines, those options were not part of GoCom.

Table 4
Participants' characteristics, ordered by potential impact on results – for the preliminary experiment and the second study.

	Preliminary study		Second evaluation study	
Characteristic	Group 1	Group 2	Group 1	Group 2
Rotations completed				
Internal medicine	5	5	13	14
Cardiology	5	4	5	6
Gastroenterology	2	3	4	3
Endocrinology			3	3
Psychiatry			11	13
Obstetrics and Gynecology			10	12
Grade point average mean and standard deviation	84.6 ± 3.3	84.2 ± 8.3	86.73 ± 6.83	87.71 ± 6.15
Native language				
Hebrew	4	4	5	4
Arabic	1		0	1
English		1	7	9
Russian			1	0
Age	29 ± 1.67	28 ± 2.1	28.69 ± 2.86	29.00 ± 2.88
Gender				
Male	2	4	5	9
Female	3	1	8	5

4.2.1. The evaluation software developed for the study

Two versions of a similar user interface were developed: a system interface in which the user-dialog window presented GoCom's recommendations and a request for the participants' feedback, and a no-DSS-mode interface that did not present recommendations, but asked participants to provide their diagnosis and all alternative management options that they were considering valid.

Appendix B presents screen shots of the two modes from the first study. In GoCom-mode UI, the problems and medications were aligned by specifying clinical goals (e.g., problem: DU; goal: secondary prevention of NSAID ulcers; medication: Long-term PPI). In the no-DSS mode, the Goals column was not presented and the medications and

problems were not aligned. The User Dialog pane (bottom-left) included instructions and places for the participants to enter their solution of the cases presented. In GoCom-mode, the participants were presented with advice and had to indicate whether they accept or decline the diagnoses and treatment/prevention options presented and they could add an explanation in case they did not agree. The User dialog for non-DSS mode included space for natural language solutions by the participants. In the second study, GoCom-mode UI consisted of option sets, as can be seen in Fig. 14.

4.2.2. Empirical study setup

The empirical assessment of the preliminary study took place in June 2019 and that of the second study took place in February 2020. The studies were approved by the Rambam Medical Center Institutional Review Board. Participation was elective, and the students who participated in the two-hour experiment earned 200 NIS (approximately $50). Students could drop out at any time and not submit their management plans. All of them completed the experiment. We advertised the experiment by writing to all sixth-year students. We asked interested students to complete a form in which they provided details regarding training, grade point average, and demographics that could potentially affect performance. These details were used to partition the students into two similar groups. Table 4 provides the participants' characteristics.

In the first empirical study, because the first two case studies were related to cardiology and gastroenterology, we considered these rotations specifically. The participants received the two case studies in the same order: Case 1 followed by Case 2. Case 1 (Hypertension, Angioedema) was given first because the correct management plan included a recommendation to stop a medication (ACEI) because it resulted in an adverse event (Angioedema). Case 2 (CVD, DU) discussed a patient whose history included stopping an Aspirin prescription. We did not want to introduce this case first so that students will not be primed to think about stopping medications. Group1 worked on odd-numbered cases without GoCom (using a similar user-interface -see Appendix B) and on even-numbered cases with GoCom. Group 2 worked on odd-numbered cases with GoCom and on even-numbered cases without GoCom. The students entered their feedback for GoCom' recommendations or their diagnosis and therapy options into the user interface.

In the second empirical study, the participants had a variety of rotations ranging from Internal Medicine, Cardiology, Gastroenterology, to Endocrinology, Psychiatry and Obstetrics and Gynecology. We balanced the two groups so that each participant would be paired with another with approximately the same rotations and grade point average. Group 1 had 13 participants, group 2 had 14 participants. Both groups received the six cases in the same order. This time the first case was introduced after the second case. The order of the cases was as follows: 2,1,3,4,5,6. Group 1 worked on cases 2,3 and 5 with GoCom and cases 1,4,6 without GoCom. Group 2 worked on cases 1,4,6 with GoCom and cases 2,3 and 5 without.

4.2.3. Methods for evaluating GoCom's perceived usefulness

We assessed GoCom's perceived usefulness by asking participants at the end of the evaluation study to answer a short questionnaire consisting of four questions. These questions included statements about the four most prominent features of GoCom for supporting medical decision making for multimorbidity patients: presenting clinical goals, presenting the option sets, presenting the overall explanation for each option set, and presenting the explanation for each goal in the option set. Participants were asked to rate these statements on a Likert scale ranging from 1 = "Strongly disagree" to 5 = "Strongly agree".

All 27 participants answered the questions.

Table 5
Results of completeness of recommendations.

Completeness	# Recommendations	DSS N per group	Mean	Mean Rank	No DSS N per group	Mean	Mean Rank	Significance (1-sided Wilcoxon Rank-Sum Test)
Pilot study: Two cases together	**16**	5	**0.71**	14.55	5	**0.44**	6.45	**0.0005**
Case 1 (Hypertension + Angioedema)	10	5	**0.72**	8.0	5	**0.38**	3.0	**0.0040**
Case 2 (CVD + DU)	6	5	**0.70**	7.1	5	**0.50**	3.9	**0.0238**
Evaluation study: All cases together	**55**	81	**0.78**	120.62	81	**0.31**	42.38	**<0.0001**
Case 2 (CVD + DU)	6	13	**0.74**	20.23	14	**0.40**	8.21	**<0.0001**
Case 1 (Hypertension + Angioedema)	10	14	**0.87**	20.50	13	**0.31**	7.00	**<0.0001**
Case 3 (Stroke + DU + Osteoporosis)	8	13	**0.77**	20.46	14	**0.35**	8.00	**<0.0001**
Case 4 (Diabetes + RFI)	10	14	**0.81**	20.50	13	**0.35**	7.00	**<0.0001**
Case 5 (Schizophrenia + Diabetes)	8	13	**0.68**	20.77	14	**0.25**	7.71	**<0.0001**
Case 6 (Pregnancy + multiple conditions)	13	14	**0.80**	20.50	13	**0.18**	7.00	**<0.0001**

Table 6
Results of correctness of recommendations.

Correctness	DSS N per group	Mean	Mean Rank	No DSS N per group	Mean	Mean Rank	Significance (1-sided Wilcoxon Rank-Sum Test)
Pilot study: Two cases together	5	0.98	11.55	5	0.91	9.45	0.167
Case 1 (Hypertension + Angioedema)	5	1.00	6.5	5	0.92	4.5	0.222
Case 2 (CVD + DU)	5	0.96	5.6	5	0.90	5.4	0.500
Evaluation study: All cases together	81	**0.83**	93.35	81	**0.68**	69.65	**0.001**
Case 2 (CVD + DU)	13	**0.89**	17.12	14	**0.65**	11.11	**0.048**
Case 1 (Hypertension + Angioedema)	14	0.87	15.29	13	0.77	12.62	0.402
Case 3 (Stroke + DU + Osteoporosis)	13	0.88	14.77	14	0.74	13.29	0.650
Case 4 (Diabetes + RFI)	14	0.74	14.68	13	0.65	13.27	0.650
Case 5 (Schizophrenia + Diabetes)	13	0.78	16.88	14	0.66	11.32	0.068
Case 6 (Pregnancy + multiple conditions)	14	**0.80**	17.32	13	**0.60**	10.42	**0.022**

5. Results of the evaluation of GoCom's Controller's functionality and usefulness

Below, we provide the results of system functionality and of the empirical studies.

5.1. Results of the evaluation of system functionality

The Controller and the user interface produced correct output for all six case studies, as compared to the defined gold standard and confirmed by the three clinician co-authors (IH, RA, and NK).

5.2. Results of the empirical evaluation of system usefulness

Characteristics of the participating students and their allocation to matched groups are presented in Table 4. All students completed the experiment.

Tables 5 and 6 present the results of completeness and correctness hypotheses, analyzed using the Wilcoxon Rank-sum test, for the pilot study and the second study. Participants identified a sixth option for Case 2 and Case 3 (Prasugrel as an antiplatelet), and an additional option for Case 5 (Clozapine as a second-generation anti-psychotic). The gold standard was extended to include these options.

The completeness hypothesis was confirmed for both studies for all cases (in each study) taken together and also when each case was considered separately. In the pilot study, there was a P-value of 0.0005 for both patient cases taken together and P-values of 0.004 and 0.0238 for the Angioedema-Hypertension and the CVD-DU cases, respectively. The mean completeness was around 0.7 when using GoCom and 0.5 or lower without GoCom. In the second, larger study, the completeness hypothesis was confirmed with P-value < 0.0001 for all cases separately and together. The mean completeness was around 0.78 when using GoCom and 0.31 without.

In the pilot study, the correctness hypothesis was rejected, as students performed correctly in most cases ($\geq$0.9) with or without GoCom. However, in the second, larger study, the correctness hypothesis was confirmed as for all cases together (P-value 0.001) and for Case 2 (P-value 0.048) and for Case 6 (P-value 0.022) separately. The correctness hypothesis was rejected for Cases 1, 3, 4, 5, as the students performed with $\geq$ 0.6 correctness in all cases even without GoCom, so use of GoCom did not result in a significant difference for those cases. However, the means of all the cases are higher when using GoCom, including those that did not show statistical significance. The overall mean correctness was around 0.83 when using GoCom and 0.68 without.

Thus, the evaluation study confirmed the improvement in completeness found in the pilot study and also confirmed the correctness hypothesis.

5.2.1. Analysis of incomplete or incorrect actions

We examined all the cases where participants did not achieve completeness or correctness. These are reported in Table 7. Three incompleteness errors occurred with or without GoCom: not indicating (or disagreeing with) all possible treatments for a given goal, leaving a goal unmet, and forgetting to replace medications that were stopped. Four types of incompleteness errors occurred only without GoCom (see Table 7). Two incorrectness errors occurred with or without GoCom (see Table 7). Three types of incompleteness errors occurred only without GoCom.

Table 7
Cases of incorrect solutions.

Error description	Without GoCom	With GoCom
Incompleteness errors		
Diagnosis not provided (angioedema in case #1, candidiasis in case #4, weight gain in case #5)	X	–
Did not recommend any treatment for a new - or condition (angioedema for case #1 and candidiasis in case #4)	X	–
Leaving a new goal unmet (potassium iodide for Diabetes Preconception-Care-Decreased Thyroid Hormone Secretion)	X	X
Unmet existing goal: Current regiments not continued for prevention (statins for CVD prevention in case #2, case #3)	X	–
Unmet existing goal: Medications that were stopped were not replaced (Aspirin (case #2, case #3), ACEI (case #1)	X	X
Monitoring not mentioned after medication switch (blood pressure monitoring in case#1)	X	–
Not all possible treatments for a given goal were indicated by participants (all cases)	X	X
Incorrectness errors		
Incorrect diagnosis (two participants using GoCom did not agree that a diagnosis of the cause of DU could be determined before results of H Pylori return. A few participants without GoCom stated a diagnosis of DU due-to H Pylori – case #2)	X	X
Suggested treatment that is not recommended, for a new problem (epinephrine, epinephrine or antihistamines for angioedema in case #1)	X	–
Suggested replacement medication that is not indicated, for a medication that had to be stopped (Replacing ACEI with Beta Blockers in case #1, replacing antiplatelets with anticoagulants, in case #3, replacing SGLT2 with Thiazolidinediones or insulin in case #4, replacing Sulfonylurea with incorrect diabetes medications in case #5)	X	–
Recommending continuing medications that is contra-indicated for a new condition (methimazole, atorvastatin, metformin and Lisinopril are teratogenic and should be stopped when planning pregnancy in case #6)	X	X
Suggesting a recommendation that is redundant as if it is a new Recommendation (suggesting a stricter diet for the patient who is already following a strict diet in case #5)	X	–

5.3. Results of GoCom's perceived usefulness

In response to the survey on their experience of using GoCom, most participants agreed or highly agreed that GoCom assisted in their decision making, that option sets were useful, and that the overall explanation of an option set and each of its goals were useful. The average rating of all these four questions were 4.1 (3.93, 4.11, 4.22, 4.15 for questions 1–4 respectively, as shown in Table 8). The vast majority of participants found all features of GoCom to be useful for their decision making on management of multimorbidity patients.

6. Discussion

GoCom provides the first implementation of a DSS system that manages multimorbidity by combining standard-based general medical knowledge, CIGs, and hierarchical goal modelling with a novel Controller algorithm that implements aggregation and explanation strategies for the mitigation of inconsistencies that occur while the patient's multiple conditions evolve over time. Goal-oriented modelling, combined with the use of metaproperties in PROforma, allows a non-rigid structure of the system that facilitates easier detection and

Table 8
Results of GoCom's perceived usefulness.

Question	Mean ± Stdev	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Presenting clinical goals assisted me in decision-making	3.93 ± 1.07	1 (3.7%)	3 (11.1%)	1 (3.7%)	14 **(51.9%)**	8 **(29.6%)**
Presenting option sets of treatment options that can be given together to address multimorbidity was useful	4.11 ± 0.80	0 (0%)	2 (7.4%)	1 (3.7%)	16 **(59.3%)**	8 **(29.6%)**
Presenting the overall explanation for each option set was useful	4.22 ± 0.85	0 (0%)	1 (3.7%)	4 (14.8%)	10 **(37.0%)**	12 **(44.4%)**
Presenting an explanation for each goal in the option set was useful	4.15 ± 0.71	0 (0%)	1 (3.7%)	2 (7.4%)	16 **(59.3%)**	8 **(29.6%)**

mitigation of inconsistencies. The management solutions provided by the mitigation pattern, as a result of reasoning combined with the patient's goal forest, are meant to guide the patient towards completion of goals rather than merely execution of tasks. The Controller algorithm that was developed in this study is generic, scalable, and reusable for multiple CIGs, as has been demonstrated by the case studies. The Guide presented in [47] was developed as part of our research and presents a refined formal modeling process to produce goal-oriented PROforma CIGs.

Our study begins to address two of the grand challenges in clinical decision support defined by Sittig et al. [64]. One, which is the main focus of this study, is combination of recommendations for patients with multimorbidity. In this stage of our research, the inconsistencies that can be detected are only of two types – starting vs. stopping medications that belong to the same medication hierarchy, and detecting opposing physiological effect goals that are specified in concurrent CIGs. However, the design of GoCom is modular and generic and allows the future introduction of additional interaction detection and mitigation strategies. The aggregation strategy developed in this study provides the physician with a full view of all possible (clinically correct) therapy combinations. The mitigation pattern that applies this strategy produces management option sets that take into account all of the patient's morbidities as well as imperfect management plans, bringing the system closer to a real-life setting.

Summarizing the patient's information in a way that would help the clinician look at the most important data points of the patient's case is another challenge presented in [64]. The explanation generation strategy is a modest contribution towards this challenge by producing explanations that convey the details as well as the idea (reasoning) behind them. The auto-generated explanations provide either guideline extracts or the system's reasoning to the clinician rather than conveying simple data and are meant to ease the understanding of the patient case and the output of the system. Further work is required to understand the nature of explanations that are desired by clinicians and the visualization that would make them clear and useful.

6.1. Studies to evaluate system usefulness

In the two studies we sought to empirically establish a proof of concept that GoCom is useful to clinicians. Participants perceived GoCom's visualization and explanations, provided in the second study, as useful for their decision making for management of multimorbidity patients. Both studies provided evidence that GoCom improves completeness. Improvement of correctness was demonstrated in the larger (second) study when all cases were considered together, and for two of the six cases separately. However, these results were not demonstrated in the other four cases and for the small pilot study. A similar effect has been observed in a single-CIG-based DSS [63,65].

Another observation is that the overall correctness (with or without GoCom) was lower in the second evaluation experiment (relative to the pilot study experiment). This could be due to the more rigid time constraints; in the pilot study, the participants had two hours to complete two cases, whereas in the evaluation experiment, participants had two hours to complete six cases.

Table 9
Comparison of Asbru goal structure with GoCom's goal structure.

GoCom Goal Trees	Asbru goals for hierarchical plans
Prevent CVD	Avoid CVD [t1, until the Complete condition of the guideline is True]
Decrease platelet-aggregation	Achieve State:decreased-platelet-aggregation [t1, t1] Maintain State:decreased-platelet-aggregation [t1, until the Complete condition of the guideline is True]
Start Aspirin	Achieve Action: Aspirin [t1, t1] Maintain Action:Aspirin [t1, until the Complete condition of the guideline is True]
Treat DU due-to NSAID	Achieve State: DU-due-to-NSAID healed [t2, t2 + 1 week]
Stop NSAID (for a week)	Avoid NSAID [t2, t2 + 1 week]
Inhibit gastric-acid-secretion	Achieve State:inhibited-gastric-acid-secretion [t2, t2 + 1 week]
Start Omeprazole	Maintain Action:Omeprazole [t2, t2 + 1 week]
Prevent DU due-to-NSAID	Avoid State: DU-due-to-NSAID [t2 + 1 week, until the Complete condition of the guideline is True]
Stop NSAID (long-term)	Avoid NSAID [t2 + 1 week, until the Complete condition of the guideline is True]
Inhibit gastric-acid-secretion	Avoid State: gastric-acid-secretion [t2 + 1 week,]
Start Omeprazole (long term)	Achieve Action: omeprazole [t2 + 1 week, t2 + 1 week] Maintain Action:Omeprazole [t2 + 1 week, until the Complete condition of the guideline is True]

An interesting observation is that the system is only as good as the guidelines that serve as its knowledge base – as can be seen by the participants suggesting new treatment options (Prasugrel and Clozapine) that are valid, yet were not included in the clinical guidelines, and therefore were not part of GoCom. Similarly, it is interesting to note that this out-of-the-box thinking was demonstrated only by participants (three of five) who were not using GoCom, consistent with other studies that noted that a DSS may make users respond to recommendations but limit their independent thinking. The fact that GoCom did not include the Prasugrel and Clozapine management options, which was part of the gold standard, penalized the completeness score of all participants who used GoCom to solve cases #2 #3, and #5.

Bates et al. [66] and Sittig et al. [64] stress the importance of evaluation of usability and addressing alert fatigue and the quality of the system's interface, as an important part of clinical decision support. In future evaluations, we will test the usability of the new user interface that presents the aggregated explanations, which was developed after the pilot study was done.

6.2. Limitations and future work

The problem of clinical decision support for multimorbidity is a complicated problem, and while we aim for our study to be as

comprehensive as possible, some aspects still remain to be improved. We identified several limitations.

One limitation is that further research is required in order to integrate the system into a clinical workflow. Our use of standard patient information models and controlled medical terminology could facilitate the integration with electronic health records (EHRs) of hospitals and care centers. Future work could build on early research by Peleg et al. who developed a Knowledge-Data Ontology Mapper, KDOM [67] that implements the Global-as-View data integration pattern in order to keep the CIG model unchanged and that defines mappings between the patient data concepts used by the CIG and EHR data items.

Workflow integration should also consider that in real life, a CIG is enacted for a patient over multiple encounters. Introducing encounters or sessions into the CIG model is a topic of future research. Furthermore, currently, the system only handles cases where there are inconsistencies. A more complete DSS will need to address the interaction between the Controller and the CIG engine for supporting cases where interactions are not happening, such as adding new patients, changing patient information, and accepting non-conflicting management plans.

Some limitations are due to choices that we made for our inconsistency detection algorithm. First, our approach for generating the goal trees and detecting and mitigating inconsistencies using the what-if look ahead (Section 3.1.2.2) does not consider the entire CIG but only the current point in time. This is because there are multiple possibilities downstream and the appropriate actions for future decisions will depend on the patient's future state, which is uncertain. However, this approach raises a limitation because a conflicted goal might occur downstream. In this case, GoCom might recommend actions for a pathway that later on would need to be retracted due to an inconsistency that would be detected downstream. For these situations, approaches that consider the entire CIG may be better suited.

Second, the goal trees include desired goals that are explicitly represented in the CIG. If a medication has some physiological effect (e.g., increased platelet aggregation) as a side effect and not as an explicit goal, this physiological effect would not be part of the CIG and the resulting goal tree. Therefore, no conflict would be detected between such medication and another medication that has an explicit opposing goal (e.g., decreased platelet aggregation). In our current system, the conflict can be detected if the medication causes a side effect because of the unspecified physiological effect, and is recognized as the cause of the side effect.

Moreover, additional important functionalities must be added to the Controller algorithm in order to produce realistic decision-making, mimicking expert reasoning patterns. The most important functionality that is yet to be implemented is the temporal aspect of care plans. Temporal knowledge representation and reasoning is necessary in many disciplines, and is especially crucial for medical decision making where the order and timing of events affects interpretation and detection of temporal patterns and where trends are recognized regularly by human decision-makers [86], especially when caring for chronic patients. Temporal specification and reasoning is key in the Asbru CIG language [15,44]. Considering the intention structure of Asbru, our goal formulation maps well to it. Prevention goals map to "avoid", treatment goals generally map to "achieve" or maintain" but can also map to "avoid", as exemplified below. Physiological effect goals map to state intentions, and leaves of GoCom's goal tree, which specify starting or stopping medications, map to Action intentions of Maintain or Avoid. Table 9 shows an example of this mapping for the case of a patient taking Aspirin for secondary prevention of CVD, who develops DU due to NSAID. The DU guideline recommends stopping NSAID temporarily (for a week) and adding PPI short term for treatment. For prevention, it recommends that if aspirin is continued, the PPI should be given long term. Note that with the temporal specification of Asbru, there might in fact be no conflict between start and stop NSAID, if the Asprin is supposed to be given in some time frame while NSAIDs are not to be given in a non-overlapping time frame. In addition, Asbru's temporal specification allows the specification of gradient abstractions such as increasing/decreasing a medication's dose which may be modelled as alternative mitigation strategies to stopping a medication.

Our future work includes implementation of patterns that would facilitate temporal mitigation such as resolution of interactions via adjustment of intake time, suspension and reactivation of management plans, consideration of medical procedures planning and the preparations that need to be done prior to them, while considering the patient's co-morbid conditions. In that implementation, we can draw ideas from the Asbru goal structure.

Additionally, we plan to implement monitoring, detection and mitigation of adverse events, which are considered a major concern in healthcare and are a complex issue that has to be considered in clinical decision support systems [68]. Monitoring may include definition of goals that avoid an undesirable patient state (e.g., avoid bleeding). We plan to link to the AEOLUS [69] database of patient-reported adverse events in order to detect and monitor adverse events.

Currently, mitigation of adverse events and inconsistencies is limited to our use of CIG knowledge and medication subsumption hierarchies. We considered using the NDF-RT also to suggest management options that are not included in the guideline but have the same treatment, prevention, or Physiological Effect Goals, and that are not contraindicated. However, our clinical experts are concerned that the details and level of evidence of the current available ontologies are not sufficient for recommending management plans that are not indicated by clinical practice guidelines. We intend to keep searching for a medical knowledge source with sufficient detail and evidence level that will supply us with alternative management plans outside the guideline.

Goal prioritization [64] and consideration of patient preferences [70] during shared decision-making are also an integral part of our future work. They will allow our system not only to provide all the information the physician needs but also to indicate, out of the possible solutions, which is the preferred one for the patient.

7. Conclusion

As demonstrated by this study, our multimorbidity goal-based framework seems feasible and can help clinicians to be more complete in diagnosis and management. Our planned future work includes extending the functionality of the Controller to detect adverse events, address temporal constraints in medications, procedures and recommendations, and to address goal prioritization and patient preferences.

CRediT authorship contribution statement

Alexandra Kogan: Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Mor Peleg:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Samson W. Tu:** Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision. **Raviv Alon:** Resources. **Natanel Khaitov:** Investigation, Resources. **Irit Hochberg:** Validation, Investigation, Resources, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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 paper.

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Appendix A:. Patient data as presented in the evaluation patient record for case study #1:

A 38-year old male was prescribed Lisinopril (ACE Inhibitor) for Hypertension. Three months later, the patient came in with symptoms of Angioedema that was eventually diagnosed as Recurrent Angioedema due to ACEI. The treatments included replacing Lisinopril with a drug from the ARB family, and prescribing medication for treatment of Hereditary Angioedema as well as preventative management and blood pressure monitoring.

Visit Date: 22/04/2019
Mr. Jack Johnson is a 38 year old male, height 177, weight 80 kg, BMI: 25.5

Problem	Goal	Medication/Action
1. Hypertension (21/02/2019)	Hypertension Monotherapy	Start Lisinopril (ACE Inhibitor) - ongoing
2. Recurrent Angioedema (13/05/2019)	Diagnosis, treatment, and prevention	

Investigations:
Results available:
Basic Metabolic panel (06/05/2019)
CBC with differential (06/05/2019)
Complement protein 4 (C4) levels (06/05/2019)
C1 inhibitor levels (06/05/2019)

Visit Log:
13/05/2019
Patient presented with a 2-hour history of swelling of his face, tongue, and lips, which is less severe than his presentation one week ago. One week ago, the patient was given Epinephrine and sent to the hospital, the symptoms subsided after two days and the patient was released. The patient had lab work done while he was in the hospital including C1-inhibitor and C4 levels which were both very low. The tests were repeated and were confirmed to be very low. Another doctor has seen the patient and concluded a diagnosis of recurrent angioedema.

06/05/2019
Patient comes in with a 4-hour history of swelling of his face, tongue, and lips. It has progressively worsened over the first 3 hours but has stabilized. Patient also complains of dyspnea for the past 2 hours. Patient states this is the first time he experienced this. Patient denies any urticaria, fever, tearing, rhinorrhea, nausea, vomiting, weakness, or dizziness. Patient denies any allergies, or stings. On physical exam his O2 saturation is 99%, respiratory exam was normal. Patient was given Epinephrine and was sent to the hospital

22/03/2019
Patient comes in for a follow up after starting Lisinopril. Patient states that he feels well. He takes his medication as prescribed and denies any orthostasis, dizziness or other side effects. He tolerates his medication well. His BP today is 126/74 mmHg and he is at goal for his blood pressure. Patient will continue with current regiment and follow up in 3-6 months

21/02/2019
Patient comes in for a follow up after being seen 1 week ago to present his home blood pressure measurements. The patient checked his blood pressure once per day and it averaged at 143/88 mmHg with all systolic blood pressure values over 140. Today his blood pressure in the clinic is 143/86. Patient is diagnosed as having essential hypertension and was advised to reduce his salt intake, exercise, and go on the DASH diet. He will also start on Lisinopril (ACEI). Patient will follow up in 1 month to reassess

12/02/2019
Patient comes in today for a routine yearly visit. He states that he has no complaints and that he feels well. Physical exam was normal. Vital signs include respiratory rate: 16/min, heart rate: 76 bpm, blood pressure: 148/85 mmHg, repeat blood pressure in 5 minutes is 146/87 mmHg. On questioning, the patient reports that his father and two of his older siblings have hypertension. Patient is advised to check home blood pressure once per day to assess for hypertension and to follow up in 1 week

Controller Dialog:
Based on the patient history (see Visit Log), the problems of Hypertension and Angioedema are shown in the Problems window and are the start of this scenario.

The decision support system is based on a clinical guideline. It recommends all option that according to the guideline are appropriate.

Please write below each decision-support recommendation "Yes" if you agree and "No" if you disagree with each recommendation. Add an explanation if you disagree.

Then indicate which alternative you finally choose and if it is not one of the options that was recommended, add an explanation.

1) The patient has one new proposed diagnosis: Hereditary Angioedema suspected: due-to ACEI
Agree? _____

Explanation _____

2) Recommendation for goal Acute Treatment of Hereditary Angioedema
Option 1: Start C1 esterase inhibitor now, single dose [proposed]
Option 1 can be considered
Agree?_____
Explanation _____

Option 2: Start Ecallantide [proposed]
Option 2 can be considered
Agree?_____
Explanation _____

Option 3: Start Icatibant [proposed]
Option 3 can be considered
Agree?_____
Explanation _____

My preferred option is: ___
Comments: _____

3) Recommendation for goal Self-treatment of Future Acute Attacks of Hereditary Angioedema
Option 1: Supply patient with emergency kit containing sufficient medication for on-demand treatment of two attacks and ask him to carry on-demand medication at all times [proposed]
Option 1 can be considered
Agree?_____
Explanation _____

4) Recommendation for goal Preventative management of Hereditary Angioedema
Option 1: Stop ACE inhibitor [proposed]
Option 1 can be considered
Agree?_____
Explanation _____

5) Recommendation for goal Hypertension Monotherapy
Option 1: Start Angiotensin II Receptor Blocker now, long-term [proposed]
Option 1 can be considered
Agree?_____
Explanation _____

Option 2: Start Calcium Channel Blocker now, long-term [proposed]
Option 2 can be considered
Agree?_____
Explanation _____

Option 3: Start Thiazide diuretics now, long-term [proposed]
Option 3 can be considered
Agree?_____

Explanation _____ My preferred option is: ___ Comment _____ 6) Recommendation for goal Hypertension Monotherapy.BP monitoring Option 1: Monitor blood pressure to ensure it is well controlled Option 1 can be considered Agree?_____ Explanation _____ Comments: _____
Expected answer for users with no DSS: Due to the patient's low levels of Complement protein 4, The suggested diagnosis is Familial Angioedema, which can be caused by Lisinopril – an ACE Inhibitor. In the patient's visit log a connection can be seen between the patient starting Lisinopril and the presentation of Angioedema. The recommended treatment is C1 esterase inhibitor recombinant. In addition Lisinopril has to be switched to a different medication that is not ACEI for example and ARB: Losartan.

The gold-standard solution includes the 6 questions above with a positive answer to all of the CIG's recommendations. Some questions have multiple valid decision options.

Case #1 Investigations:

Basic Metabolic Panel

Calcium, serum	10	9.0-11.0 mg/dL
Creatine kinase	20	10-105 U/L
Creatinine, serum	1.2	0.7-1.5 mg/dL
Electrolytes, serum		
Sodium	141	136-146 mEq/L
Chloride	98	96-106 mmol/L
Potassium	3.8	3.5-4.5 mEq/L
Bicarbonate	24	22-29 mEq/L
Glucose, serum (random)	145	80-200 mg/dL
LDH	55	45-90 U/L
Magnesium, serum	1.4	1.3-2.1 mEq/L
Osmolality, serum	290	285-295 mOsm/kg water
ALP	40	20-90 mU/mL
Phosphorus, serum	4.1	3.0-4.5 mg/dL
BUN	15	11-23 mg/dL
Uric acid, serum	3.1	2.6-7.2 mg/dL

CBC Differential

Erythrocyte count, blood	5.2	4.6-6.2 million/mm^3
Hematocrit	45	40-54%
Hb	15	14.0-18.0 g/dL
Leukocyte count	8000	4500-11,000/mm^3
Segmented neutrophils	58	54-62%
Bands	4	3-5%
Eosinophils	2	1-3%
Basophils	.5	0-0.75%
Lymphocytes	28	25-33%
Monocytes	4	3-7%
MCH	28	27-31 pg
MCHC	35	33-37 g/dL
MCV	85	80-96 µm3
Platelet count, blood	210,000	150,000-350,000/mm^3
RDW	9	≤ 14.5%
Reticulocyte count	.8	0.5-1.5% of erythrocytes

Inflammatory markers

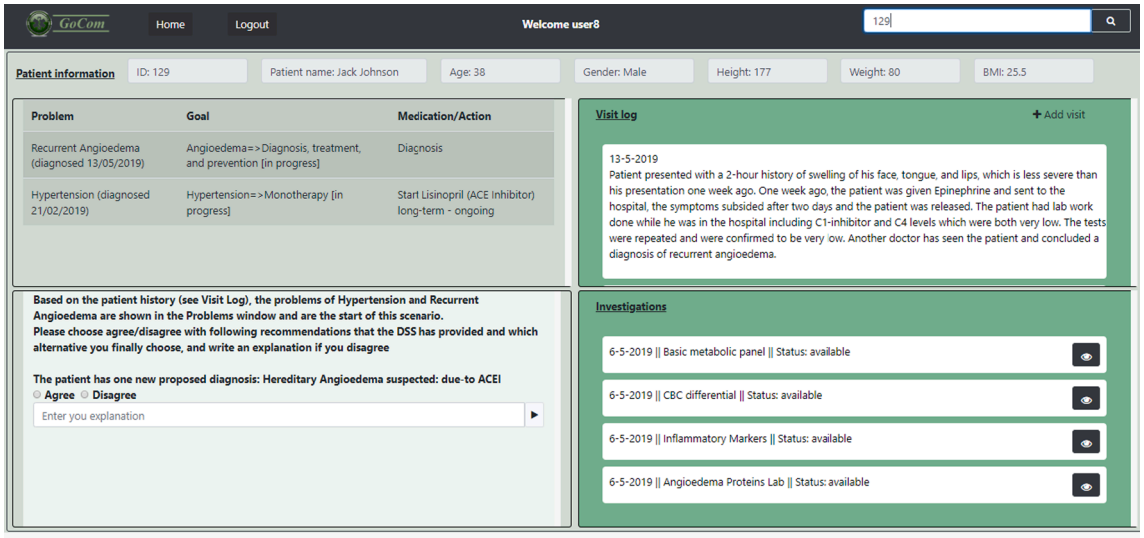
ESR	8	0-15 mm/hr
CRP	2	0-10mg/dL

Angioedema Proteins Lab

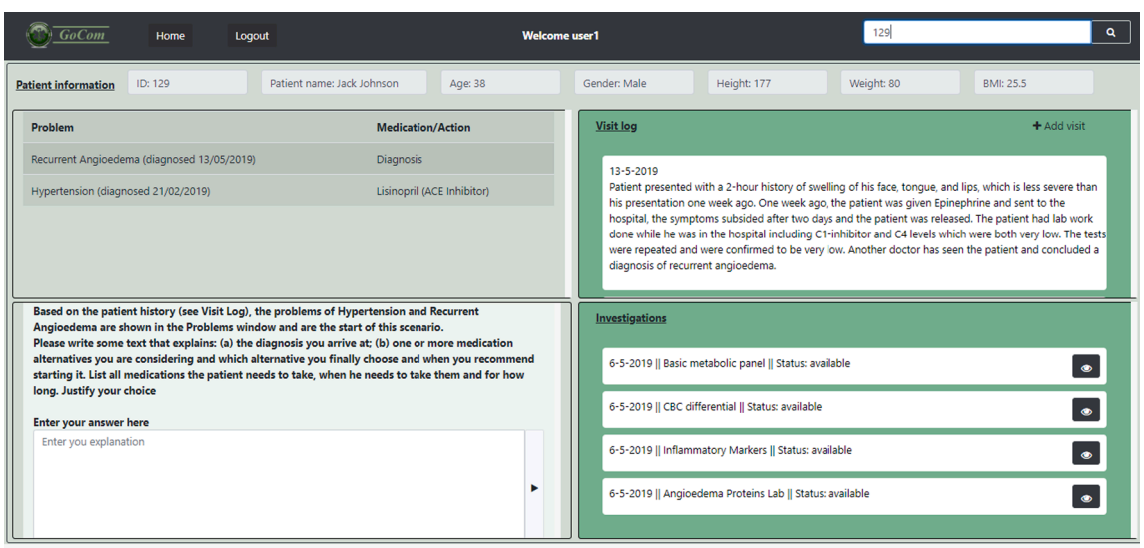
C4 protein	6 ↓	16-48 mg/dL
C1 esterase inhibitor protein	8↓	21-39 mg/dL

Appendix B. Screenshots of the system presented to the users during evaluation

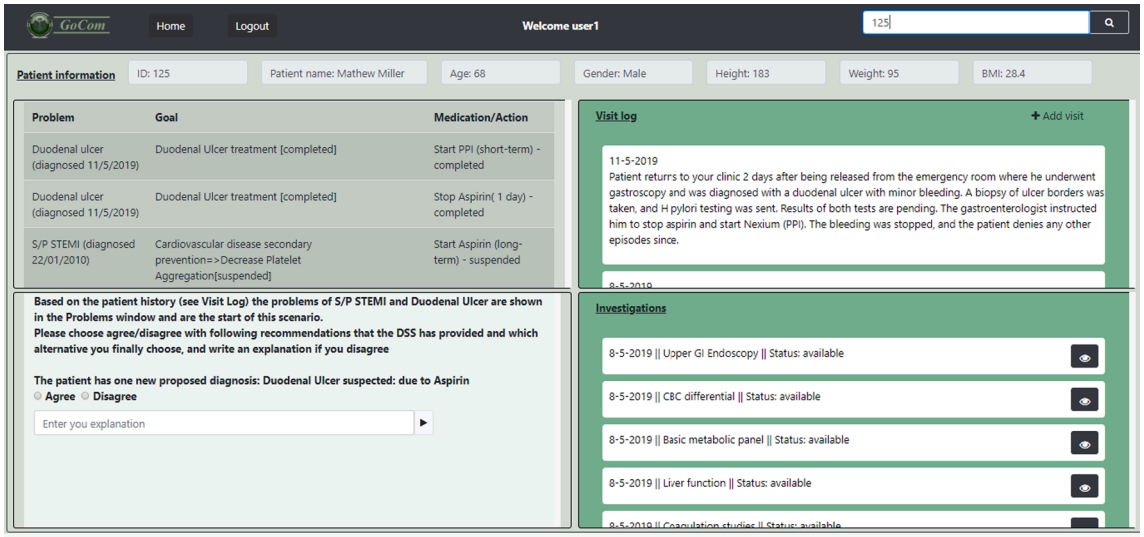
Case #1 with DSS



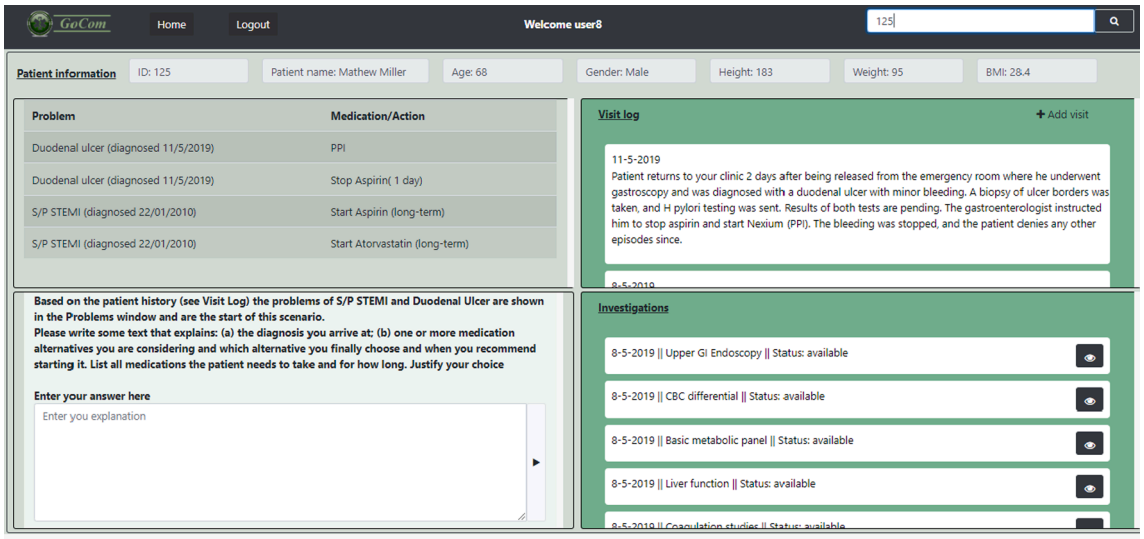
Case #1 without DSS



Case #2 with DSS



Case #2 without DSS



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