Guideline Representation Ontologies for Evidence-based Medicine Practice

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An ontology in the context of guideline representation is a specification of conceptualizations that constitutes evidence-based clinical practice guidelines. It represents the elements of a guideline by specifying its attributes and defining the relationships that hold among them. For example, a guideline representation ontology would define a set of medical decisions and actions (concepts), as well as a set of rules (relationships) that relate the evaluation of a decision criterion to further reasoning steps or to its associated actions. A rigorously defined computational ontology provides considerable promise of producing computable representations that can be visualized, edited, executed, and shared using computer-based systems. A widely acknowledged ontology, or standard representation schema, is the key to facilitating the dissemination of guidelines across computer systems and healthcare institutions.

The first part of this chapter presents the evolution of ontology research in guideline representation. Several representative ontologies are reviewed and discussed, with in-depth analyses of two popular models: GLIF (Guideline Interchange Format) and PROforma. The second part of the chapter analyzes seven key elements constituting a guideline representation. It also discusses the criteria for evaluating competing ontologies and some known limitations in the existing models. At the end of this chapter, four key steps are outlined that converts a guideline into computerized representation, which can be then used in Clinical Decision Support Systems (CDSSs).

1 Introduction

Evidence-based medicine is “the conscientious, explicit, and judicious use of current best evidence in making medical decisions about the care of individual patients” [14]. Evidence-based clinical practice guidelines, a condensed form of evidence-based medicine, are published and maintained by professional
organizations. For example, the National Guideline Clearinghouse currently hosts over 1,700 active guidelines, spanning a wide variety of disease areas and conditions. However, these guidelines are usually prepared and disseminated as unstructured, descriptive textual documents that are primarily intended for human readers, inhibiting their automated use within Clinical Decision Support Systems. In addition, the lack of a standard schema also impairs the interoperability of guideline representations, resulting in a waste of implementation time and resources, and potentially increased error rates. To alleviate the problem, the development of standard, structured guideline representation ontologies is of vital importance.

The contemporary usage of the term ontology is derived from its much older usage in philosophy, in which it studies existence, its component entities, and the relationships between them. A contemporary ontology can be defined as “a formal, specific conceptualization of a domain; by adopting an ontology, an agent makes an ontological commitment to use only the vocabulary the ontology provides, and to use it only to denote the concepts provided” [6]. This definition articulates the concepts existing in a domain as well as its taxonomy, rules, and the relationships existing between them. These concepts are usually abstract, simplified views of the knowledge existing in a domain, such as medicine or biology. They do not necessarily represent complete knowledge of that domain, but can be composed of a subset, required for a specific application.

The main purpose of introducing the concept of ontology into knowledge representation is to enable knowledge sharing and reuse. Rigorously defined ontologies—with computer-recognizable semantics and structure that support some level of computation—are called computational ontologies. Computational ontologies are pivotal component of computer systems designed for intelligent reasoning, for example, Clinical Decision Support Systems.

The concept of ontology has been widely adopted in many disciplines such as computer science, information science, medicine, and genomics. Well known examples are 1) the semantic web ontologies that provide a universally accessible platform for data to be shared and processed by automated tools over web; and 2) the gene ontologies that provide controlled vocabularies to de-

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5 http://www.guideline.gov/.

6 The concept of ontology pervades our life. For example, a natural language is analogous to an ontology, in which nouns and verbs are concepts and grammar defines the relationships. A taxonomy or hierarchy is also a simple kind of ontology, in which concepts are arranged according to only one relation: “is a kind of”.

7 Web Ontology Language (OWL) is an ontology that facilitates information sharing between intelligent applications (instead of just presenting information to humans). It explicitly represents the meaning of terms in vocabularies and the relationships between those terms. It is a standard under development by W3C. http://www.w3.org/2001/sw/.
scribe gene and gene product attributes in any organism\(^8\). Not surprisingly, every knowledge-base or knowledge-based expert system should implement an ontology, explicitly or implicitly \([6]\).

In the context of clinical practice guideline representation, an ontology is a specification of concepts and relationships that constitute an evidence-based clinical practice guideline. It conceptualizes the elements of a guideline, their properties, and defines the relationships that hold among them. For example all guideline representation ontologies have a set of medical decisions and relevant actions (concepts), and a set of temporal rules that relate decision evaluation results to associated actions (relationships). A well established and generally acknowledged guideline representation ontology ensures that the resulting representations can be easily understood by non-authoring human readers, therefore facilitates the dissemination of guidelines across institutions. Well defined computational ontologies also provide considerable promise of enabling automated guideline acquisition, visualization, execution, and sharing. Such characteristics are prerequisites for a computer-recognizable, interchangeable guideline format. Without these features, it is difficult to enable automated knowledge acquisition and execution for Clinical Decision Support Systems designed to enhance evidence-based practice \([20,21]\).

2 Existing Guideline Ontologies

2.1 The Evolution of Guideline Ontologies

There have been numerous efforts to represent medical knowledge to support computerized decision support. Among them, the Arden Syntax introduced in 1989, was the first and has become a certified standard of HL7\(^9\). Arden Syntax provides a specification for encoding medical knowledge as individual rule-based procedures, also known as Medical Logic Modules (MLMs). These MLMs each contains sufficient logic to make a single medical decision. Arden Syntax, however, is not designed to represent comprehensive clinical practice guidelines. It is up to the adopter’s judgment to link individual MLMs in order to construct complex logic representing a full guideline. Extensions of Arden Syntax have been developed to accommodate this limitation, for example Interacting MLMs \([7]\), which specifies how to use multiple MLMs as

\(^8\) Gene Ontology (GO) is an ontology that facilitates information sharing and machine reasoning, by providing a controlled vocabulary for the description of cellular components, molecular functions, and biological processes. It is a standard under development by Open Biological Ontologies (OBO). [http://www.geneontology.org/GO.doc.shtml](http://www.geneontology.org/GO.doc.shtml).

\(^9\) Health Level Seven (HL7) is an ANSI accredited standards developing organization in the health domain. It is an international community of healthcare subject matter experts and information scientists collaborating to create standards for the exchange, management and integration of electronic healthcare information. [http://www.hl7.org/](http://www.hl7.org/).
a set to mimic guideline behavior; and Augmented Decision Tables, which implements algorithms for additional capacities, such as probabilistic reasoning [16]. Nevertheless, it has been a well known issue that the Arden Syntax is inadequate to represent complex guidelines that have advanced medical decision algorithms or multiple steps that unfold over time [13].

This realization has led to the development of more comprehensive models. Among them well known and still existing ones include Asbru, EON, GLIF (Guideline Interchange Format), and SAGE (Sharable Active Guideline Environment), developed in the United States; and GASTON, GUIDE, PRODIGY and PROforma, developed in Europe. Some of these ontologies, such as GLIF and SAGE, aim to achieve a general, interchangeable format; others such as PRODIGY3, focus on representing guidelines in certain disease areas such as chronic disease management and preventive care procedures.

Most of the existing guideline ontology models were independently developed. Nevertheless, they share many common characteristics, reflecting synthesized views of prior modeling work as well as the inherent nature of the evidence-based clinical practice guidelines these models attempt to represent [13]. While distinct design choices are made along many dimensions, ultimately these efforts attempt to achieve an guideline representation ontology that can:

- Represent and execute various types of guidelines with varying levels of complexity;
- Efficiently represent guidelines with minimal, reusable constructs;
- Provide visual tools that allow non-expert users to directly create, modify, compile, and execute computer algorithms that implement clinical practice guidelines;
- Support seamless integration with heterogeneous CDSSs for automated guideline execution;
- Provide a mechanism to minimize the amount of work in adapting generic guideline representations to intuitional requirements or other local contexts.

Because of many common shared characteristics, the existing models are reasonably interchangeable. Researchers have shown that a generic comparison model can be developed in order to map different guideline representation models to a set of generalized guideline execution tasks [13]. Being aware of the existence of such common characteristics, newly initiated projects, such as SAGE, aim to develop mechanisms to inherit the relevant features of existing ontologies to achieve a unified format for guideline representation.

In the next section we review several representative guideline ontology models: GLIF, SAGE, PROforma, EON, PRODIGY, Asbru, and GUIDE. Two popular models, GLIF and PROforma, are also selected for in-depth analyses.
Major Ontologies in Use

Approximately thirty ontologies have been developed for representing and executing medical knowledge. The ontology models included in this section are typically comprehensive ontologies that can be used to represent a full guideline. Information contained in this section is obtained from research publications or the project websites of these ontologies, unless otherwise specified.

GLIF

Unlike many other ontologies, the principle motivation for the development of the Guideline Interchange Format (GLIF) is to achieve a standard, sharable language for modeling and disseminating clinical practice guidelines. GLIF is developed by the InterMed Collaboratory, a joint project of the medical informatics laboratories at Harvard, Stanford, Columbia, and McGill Universities. Its research and implementation work is currently overseen by the HL7 Clinical Guidelines Special Interest Group. The first published version of GLIF, version 2, was released in 1998. The latest one, version 3, was released in 2000. An in-depth analysis of the GLIF3 format is presented in Section 3.2.

Tools: GLIF uses Protégé as its authoring tool\(^{10}\). GLIF3 develops an object-oriented query and expression language, GELLO, for encoding medical decisions. The GLIF3 Guideline Execution Engine (GLEE) is the tool for executing the guidelines encoded in the GLIF3 format.

Implementation: GLIF3 encoded guidelines are being used at Columbia University for post-CABG (Coronary Artery Bypass Grafting) patient care planning. A diabetes foot guideline is used in Israel at several primary care outpatient clinics.

URL: http://www.glif.org/

SAGE

Similar to GLIF, the SAGE (Sharable Active Guideline Environment) is proposed to inherit features of the existing ontologies as well as established medical standards to achieve a mechanism for interoperable distribution of guideline-based decision support systems. The ultimate goal of SAGE is to create an infrastructure that allows guideline execution across heterogeneous clinical information systems. The project started in 2002, as a collaboration between the IDX Corporation, Stanford Medical Informatics, Mayo Clinic (Rochester), the University of Nebraska, Intermountain Health Care, and

\(^{10}\) Protégé is an open source ontology editor for constructing domain models and knowledge-based applications with ontologies, maintained by Stanford University. http://protege.stanford.edu.
Apelon. The most recent internal release is version 1.57, updated in September, 2005 [18].

**Tools**: SAGE also uses Protégé as its authoring tool, with a customized plug-in called Kwiz that extends Protégé's ability for guideline modeling in SAGE.

**Implementation**: SAGE encoded guidelines have not been used in practice; nevertheless there are plans to use SAGE to implement guidelines for immunization, diabetes, and community-acquired pneumonia in simulated environments at Mayo Clinic and University of Nebraska Medical Center.

URL: [http://sage.wherever.org/](http://sage.wherever.org/)

**PROforma**

PROforma aims to provide a specification and a knowledge representation language for authoring, publishing, and executing clinical guidelines. It is developed at the Advanced Computational Laboratory of Cancer Research in the United Kingdom. Starting in 1999, PROforma was commercialized by InferMed Ltd, under the brand name Arezzo. PROforma is essentially a first-order logic (FOL) formalism\(^{11}\) to support medical decision making and plan execution. In addition, it supports a number of non-classical logics, such as temporal logic. An in-depth analysis of the PROforma is presented in Section 3.3.

**Tools**: Tallis Composer is developed to author and execute guidelines encoded in the PROforma format. It is available at no charge for collaborative research use. Arezzo, a commercial product, provides dedicated authoring and execution environment for PROforma.

**Implementation**: PROforma has been used to develop a wide range of prototype and routinely used clinical applications. Some examples are CAPSULE, providing advice on prescribing in general practice, and Bloedlink, providing advice on laboratory tests, management of chronic diseases such as dyspepsia, asthma, and depression.

URL: [http://www.acl.icnet.uk/lab/proforma.html](http://www.acl.icnet.uk/lab/proforma.html)

**EON**

EON is a guideline representation ontology that seeks to “create an architecture made up of a set of software components and a set of interfaces that

\(^{11}\) First-order logic, or first-order predicate logic, is symbolized reasoning in which each sentence, or statement, is broken down into a subject and a predicate. The predicate modifies or defines the properties of the subject. First-order logic is very useful in the creation of computer programs for in artificial intelligence reasoning.
developers can use to build robust decision-support systems that reason about guideline-directed care” [8]. It was developed by Stanford Medical Informatics. The project was initiated in 1996, ended in 2003, and the results are carried over to the SAGE project. Its guideline model, called *Dharma*, defines guideline knowledge structures such as eligibility criteria, abstraction definitions, guideline algorithms, decision models, and recommended actions. The EON execution system obtains patient data through a specified temporal database manager or from user input, and then generates guideline based recommendations.

**Tools:** EON uses Protégé as its authoring tool. *Padda* is the environment for executing guidelines encoded in EON, based on CORBA\textsuperscript{12} architecture in a client-server fashion.

**Implementation:** EON is mainly used in the ATHENA project\textsuperscript{13} to provide hypertension advisories at a number VA sites. An application called T-HELPER (Therapy-Helper) also uses EON for data management of patients with HIV.

**URL:** \url{http://www.smi.stanford.edu/projects/eon/}

### PRODIGY

PRODIGY (Prescribing RatiOnally with Decision Support In General Practice study) is a clinical decision support system that integrates with the commercial primary care information systems in the UK. It is developed by the Sowerby Centre for Health Informatics at Newcastle. PRODIGY aims to facilitate knowledge engineering by producing a simple, understandable model sufficiently expressive in order to represent chronic disease management guidelines. PRODIGY I includes a guideline representation model, which was used in PRODIGY II to implement guidelines for the management of acute diseases. PRODIGY3 is designed to model guidelines for more chronic diseases management areas.

**Tools:** PRODIGY uses Protégé as its authoring tool. Dedicated PRODIGY3 execution environments are required in local adaptation.

**Implementation:** PRODIGY3 has been used in the UK to implement several chronic disease guidelines including hypertension, asthma, and angina.

\textsuperscript{12}CORBA (Common Object Request Broker Architecture) is an Object Management Group (OMG) standard that enables software components written in multiple computer languages and running on multiple computers to interoperate.

\textsuperscript{13}ATHENA (Assessment and Treatment of Hypertension: Evidence-Based Automation), a research project conducted by Stanford Medical Informatics and several participating VA hospitals.
Asbru

Asbru was developed as part of the Asgaard project by the Vienna University of Technology and Stanford Medical Informatics. It is a time-oriented, intention-based, skeletal plan-specification representation language to embody clinical guidelines as skeletal plans. These skeletal plans are typically used by human executing agents other than the original plan designer, although they also provide promise to represent guidelines in a computable format [15].

Tools: AsbruView is a graphical tool that supports visualization and understanding of Asbru encoded guidelines. CareVis is an integrated visualization of Asbru guidelines and temporal patient data. Finally DELT/A is a tool to edit Asbru guidelines in XML format, and to link to the original HTML guideline documents.

Implementation: Asbru has been used in the Asgaard project to create prototypes for a number of guidelines such as diabetes, jaundice, and breast cancer.

GUIDE

GUIDE is a component-based, multi-level architecture that is designed to represent and execute guidelines with both workflow management systems and EMR technologies. GUIDE is developed by the Laboratory for Medical Informatics, Department of Computer and System Science at the University of Pavia, Italy. The GUIDE framework includes a Virtual Electronic Medical Record (vEMR)\textsuperscript{14} and a logging system that allows all details of the health care process to be traced.

Tools: Guide Editor is a tool for editing guidelines encoded in GUIDE format.

Implementation: GUIDE is used in an application to support management of stroke patients in four hospitals in the Lombardia region. An application to support the management of patients with heart failure is being evaluated by general practitioners in the Trentino Alto Adige region.

URL: http://www.asgaard.tuwien.ac.at/

\textsuperscript{14} vEMR is an abstract collection of patient care related information. It is a widely adopted concept to enable data exchange across health care applications, and platform-independent application development.
3 Two Ontologies in Depth

In this section we will take a closer look at two of these seven ontologies. These two ontologies are selected because 1) they are comprehensive ontologies that can be used to represent a full guideline; 2) they significantly leverage on prior modeling work; 3) they are under continued development; 4) they are balloted to be standards under auspices of standard organizations such as HL7; and 5) they are being used, or under evaluation, to implement evidence-based guidelines in practice.

A number of comparison studies have been conducted to examine the differences and common characteristics of the existing models [11,13,20]; among these studies the Peleg et al’s paper on comparing computer-interpretable guideline models [13] is most widely cited. In the paper the authors compared several competing models, including Asbru, EON, GLIF, GUIDE, PRODIGY, and PROforma. The authors concluded that all current guideline ontologies attempt to “hierarchically decompose a guideline into networks of component tasks that unfold over time, and define rules and relationships, typical temporal sequences, among these component tasks” [13]. The resulting representations usually consist of networks of component tasks and the ability to express various arrangements of these components and interrelationships between them, also known as Task-Network Model (TNM). In Peleg et al’s paper the side-by-side comparisons were conducted among eight dimensions: organization of guideline plans, representation of goals or intentions, representation of guideline actions, models of decision-making, expression language, data interpretation, medical concept model, and patient information model. The authors concluded that consensus was found along a number of dimensions including plan organization, expression language, conceptual medical record model, medical concept model, and data abstractions; differences were most prominent in their underlying decision models, goal representation, use of scenarios, and structured medical actions [13].

3.1 Analysis Dimensions and Evaluation Criteria

In this section we extend the analysis of GLIF (GLIF3 primarily) and PROforma to include additional dimensions that reflect key components found common across major guideline ontology models. In representing clinical guidelines in a clinical decision support system, we found that these dimensions are essential to the effectiveness and feasibility of implementing an ontology model in practice. These dimensions are:

- **Level of Knowledge Acquisition**: Steps from acquiring medical knowledge from guideline publications to modeling and executing the computerized representations within heterogeneous computer systems;

- **Component Tasks**: Specification of concepts that constitute a guideline representation;
• **Expression Language**: Specification of how to express various concepts in a computer-recognizable format, with rigorously defined semantics and structures;

• **Medical Concept Model**: A layer that enables an ontology model, or its execution engine, to acquire patient data in order to provide case-specific advisories. The patient data may be coded using different medical controlled vocabularies;

• **Automated Execution**: The ability of supporting automated execution of the guideline representations;

• **Level of Sharing**: At what level the encoded guidelines can be shared: at the design level as conceptual representations, at the encoding level as sharable, computer-recognizable documents, or at the execution level that allows software agents to interact over networks;

• **Tools**: Tools developed or used for authoring, visualizing, executing, and disseminating guideline representations;

• **Applications**: Applications implemented in practice that use these ontology models to represent and execute evidence-based clinical practice guidelines;

• **Limitations**: Limitations that may prevent the wide-spread use of an ontology model. In particular we examine a model’s ease of use, amount of work required for local adaptation, and its track record of being used and evaluated in practice.

For a guideline ontology model to be successful, it must be 1) comprehensive, so it can be used to map out complex clinical guidelines; 2) efficient, so a guideline representation can be derived through a small number of steps with a small number of conceptual constructs; and 3) flexible, so that the resulting representations can be easily localized or further modified. To assess the completeness, efficiency, and flexibility of an ontology model, we developed the following evaluation criteria used for the in-depth analyses:

1. Whether the model can be incorporated into computer-based systems for effective clinical decision-support;
2. Whether the model is comprehensive enough to represent complex guidelines, such as diabetes treatment recommendations;
3. Whether the model is simple enough to represent guidelines with minimal constructs;
4. Whether the model allows clinicians with no advanced programming knowledge to revise and customize the guideline representations. The updated guidelines should be executable in a hosting decision support system with no or minimal reconfiguration;
5. Whether the model provides an execution environment that supports automated guideline execution;
6. Whether exchange of guidelines can be performed at the execution level, i.e., computerized guideline representations can be directly shared across execution environments. It should also provide a mechanism to facilitate communications across execution environments;

7. The amount of work needed in local adaptation. To minimize the localization effort, the model should provide an abstract layer that separates site-specifics from generic guideline representations\(^\text{15}\);

8. Whether the resulting guideline representations can be used for different purposes, for instance issuing physician-oriented reminders or generating administration-oriented reports for quality assurance;

9. Whether the model supports established medical terminologies and standards. It should also be extendable in order to accommodate future terminologies and standards;

10. The model should leverage the existing guideline modeling methods.

### 3.2 GLIF3

GLIF3 is the most recent release of GLIF, the Guideline Interchange Format. This in-depth analysis is conducted based on GLIF-related research publications [1,2,9,10,19], and the GLIF3 Specifications available at the GLIF project website (http://www.glif.org/).

**Overview**

GLIF3, developed by the InterMed Collaboratory, is a specification for structured representation of guidelines that aims to facilitate sharing of clinical guidelines [9]. The objective of the GLIF3 specification is to provide a representation for guidelines that is precise, unambiguous, human-readable, computable, and independent of computing platforms. The goals of GLIF3 are to 1) enable viewing of GLIF3-formatted guidelines by different software tools, and 2) enable adapting the guidelines to a variety of local uses [12]. A sample guideline diagram modeled with GLIF3 is shown in Figure 1\(^\text{16}\).

**Level of Knowledge Acquisition**

GLIF3 enables guideline knowledge acquisition at three levels: 1) *Conceptual Flowchart*, a human-readable flowchart of clinical decisions and actions that captures the essence of a guideline specification, typically prepared by medical experts; 2) *Parseable Specification*, typically encoded by GLIF3 informaticians

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\(^{15}\) One time local adaptation to reflect site-specifics may be required; however, the model should minimize the local adaptation effort by allowing configurable site profiles.

Fig. 1. Sample Guideline Diagram Modeled with GLIF3

to define details of the representation such as patient data types, algorithms of each medical decision, and clinical recommendations (this level of specification can also be used to verify logical consistency and completeness of a guideline representation); and 3) Implement-able Specification, comprising none-shareable, institution-specifics, which can be used in local adaptation to map guideline logic and instructions to the medical records stored in an operational clinical information system.

Component Tasks

In GLIF3, guidelines are represented as flowcharts of temporally sequenced nodes called Guideline Steps. Different classes of guideline steps are used for modeling different constructs. Nesting of steps is allowed, which is used to represent recursive specifications of actions and decision. The guideline steps consist of:

- **Decision Step**: Used to represent medical decisions contained in a guideline, for example “check to see whether the patient’s recent cholesterol test is under 160 mg/dL”. A hierarchy of decision classes provides the ability to represent different decision models. A decision step has a Name attribute, describing the criterion in text, and a Specification attribute, specifying the decision criterion in a formal expression language;

- **Action Step**: Use to represent actions to be performed, typically medical recommendations. An action step can be either automated ones (Case Steps), or ones that have to be made by a physician or other health worker (Choice Steps);

- **Branch Step and Synchronization Step**: Used to model multiple simultaneous paths through the guideline. A branch step directs flow to one or more of a number of guideline steps, according to a non-Boolean selection method. A synchronization step is used in conjunction with branch steps.
to synchronize flow of control through multiple, possibly parallel paths. When the selection method on a branch step is parallel, the synchronization step is placed further along each possible path exiting the branch step, in order to resynchronize the flow of control before additional steps in the guideline can be visited;

- **Patient State Step**: Entry point into a guideline, which also allows for labeling distinct patient states;

- **Macro Step**: A special class whose attributes define the information that is needed to instantiate a set of underlying GLIF3 steps that represent a pattern appeared in guidelines.

The GLIF3 classes above are specified using Unified Modeling Language (UML) class diagrams. Additional constraints on represented concepts can be described using Object Constraint Language (OCL), a subset of the UML standard. The Resource Description Framework (RDF) is the infrastructure the GLIF3 uses for the encoding, exchange, and reuse of structured metadata.

Besides the classes mentioned above, GLIF3 also introduces several new concepts, such as **Iterations** and **Conditions** that control the iteration flow, **Events** that trigger guideline steps, **Exceptions** that handle exception conditions, and a keyword **Didactic** for adding keywords to the constructs.

**Expression Language**

GLIF3 has its own expression language, GELLO, which is an object-oriented expression language derived from the logical expression grammar of Arden Syntax. GELLO can be used for representing logical criteria, numerical expressions, temporal expressions, and text string operations. GELLO has been balloted to be an HL7 accredited standard in 2004.

**Medical Concept Model**

GLIF3 has three layers for acquiring patient data from institutional information systems. The first layer, **Core GLIF**, defines a standard interface to medical data items and the relationships among them. The second layer, the **Reference Information Model (RIM)**, defines the basic data model for representing medical information needed in specifying protocols and guidelines. It includes high-level classification concepts, such as medications and observations about a patient, as well as their attributes, such as units of a measurement and dosage for a drug and other medical concepts and medical data may have. GLIF3’s RIM uses HL7 Reference Information Model17, also known as

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17 HL7 Reference Information Model (HL7 RIM) expresses the data content needed in a specific clinical or administrative context and provides an explicit representation of the semantic and lexical connections that exist between the information carried in the fields of HL7 messages.
the Unified Service Action Model (USAM). The third layer, Medical Knowledge Layer, is still under development. It will specify the methods for interfacing with controlled vocabularies, medical knowledge bases, and heterogeneous EMRs.

**Automated Execution**

The GLIF3 Guideline Execution Engine (GLEE) is the execution environment for executing GLIF3 encoded guideline representations. It is built as a middleware that can be integrated with clinical information systems at a local institution. However, the flexibility and generality of GLEE, and its capacity of being integrated with local infrastructures, have not yet been adequately evaluated. Integration of GLEE with a specific event monitoring application or computerized physician order-entry system is not supported.

**Level of Sharing**

In GLIF3 the Parseable Specification results in a structured format that can be directly shared. However, local adaptors need to convert this level of specification to an Implementable Specification in order to integrate the guideline representations with local workflow and institutional information systems. The guideline execution engine, GLEE, is still in its primitive development stage and sharing at the execution level is not available. The developers of GLIF3 have set this level of sharing as their next project target.

**Applications**

GLIF3 and GLEE are being used at Columbia University to reinforce the guideline coherence for post-CABG (Coronary Artery Bypass Grafting) patient care planning. They are also used to implement a diabetes foot guideline at several primary care outpatient clinics in Israeli. The integration of GLIF and GLEE with the clinical information system at the New York Presbyterian Hospital for clinical event monitoring is currently being explored.

**Limitations**

While GLIF3 is the most comprehensive guideline representation ontology currently available, it remains an experimental language with inadequate support of automated execution and lack of proven capacity of integration with institutional information systems. Although GLIF3 aims to define a standard for the computer-interpretable, sharable format, it has not yet been adopted by the vast health informatics community. To date GLIF3 and its execution engine, GLEE, are only used in prototype demonstrations in research settings.

GLEE, the GLIF3 Guideline Execution Environment, has been developed to facilitate execution of GLIF3-encoded guideline representations; however,
it is still in the development stage and does not assure guideline sharing at the execution level. The value of having a standard, interchangeable format is largely diminished if tremendous work will be involved in local adaptation. This problem is not unique to GLIF though. It has been a widely acknowledged issue that reflects the lack of standard medical terminologies and communication protocols. HL7 and other standard developing organizations have made considerably efforts to address the issue. With the concept of Virtual Electronic Medical Record (vEMR), the release of HL7’s new RIM standard, and other alternative technologies such as Unified Medical Language System (UMLS), the problem may be eventually solved. However, how to integrate ontology models with heterogeneous clinical information systems remains a challenge.

3.3 PROforma

We analyze the PROforma ontology based on the project’s academic publications [3–5, 17] and the PROforma language specifications available at http://www.acl.icnet.uk/lab/proforma.html.

Overview

PROforma, developed at the Advanced Computational Laboratory of Cancer Research in UK, is a formal knowledge representation language designed to capture the content and structure of a clinical guideline in a form that can be interpreted by a computer. It has been successfully used to build and deploy a wide range of decision support systems, guidelines and other clinical applications [17]. PROforma is essentially a first-order logic (FOL) formalism extended to support decision making and plan execution. In addition it supports a number of non-classical logic, such as temporal logic and modal logic, and two novel logic, LA, Logic of Argument, and LOT, Logic of Obligation and Time.

Applications built using PROforma can be used to support the management of medical procedures and clinical decision making at the point of care. The InferMed Ltd has commercialized PROforma under the brand name Arezzo. This product has been successfully implemented in practice and has been integrated in many European EMR systems. InferMed Ltd’s current clients include Hoffman la Roche, the European Society for Cardiology, and the European Society for Research in the Treatment of Cancer.

The goals of the PROforma development are to achieve a guideline representation language 1) be sufficiently expressive to fully represent a range

18 Unified Medical Language System (UMLS) is a software tool designed to facilitate the development of computer systems for use of terminologies of biomedicine and health. It is used by system developers in building or enhancing electronic information systems that create, process, retrieve, and aggregate biomedical and health data and information. http://umlsinfo.nlm.nih.gov/.
of clinical processes; 2) be sufficiently general to describe processes in any clinical specialty; in addition it 3) use concepts that are intuitive for clinical users; 4) processes specified in the language can be enacted by machine; 5) the semantics of the language are demonstrably sound; and 6) applications can be automatically checked for consistency and other properties.

Level of Knowledge Acquisition

Converting a guideline into a PROforma representation takes three steps. First a high level diagram that describes the outline of guideline (in terms of set of tasks) is developed. Next, this graphical structure is converted into a database, with detailed procedural and medical knowledge required to execute the guideline. Finally, the resulting computerized clinical guidelines are tested and executed using a PROforma-compatible engine, such as Arezzo Performer.

Component Tasks

PROforma decomposes a clinical guideline hierarchically into task networks representing plans or procedures carried out over time. Logical constructs, such as situations, constraints, pre- and post-conditions, allow the details of each task and inter-relationships between the tasks to be defined. The PROforma model classifies tasks into four different classes: Plans, Decisions, Actions, and Enquiries.

- **Plans**: Sets of tasks to be carried out to achieve a clinical goal. Plans are the basic building blocks of a guideline, and may contain any number of tasks of any type, including other plans;

- **Decisions**: Points at which choice has to be made, such as a choice of investigation, diagnosis or treatment. A PROforma decision task defines the decision options, relevant information, and a set of argument rules which determine the options to be chosen according to current data values;

- **Actions**: Procedures that need to be executed in the external environment, such as the administration of an injection or updating a database. An action can be either an operation to be performed by a person, or SQL statements that describe data manipulation procedures in a database, along with identifying information of the database in which the action is to be performed;

- **Enquiries**: Represent information needs to be acquired from a person or an external source. Enquiries may be associated with the location of a database and SQL queries that can return desired data. If automated information acquisition is not available, some external human or software agent must take the appropriate action.
All PROforma tasks have several common attributes, including Pre-Conditions: logical conditions that must be true in order for the task to start; Post-Conditions: logical conditions that may be assumed to be true after the task has finished; Goal: a logical condition expressing the situation that the task is intended to bring about; Caption and Description: documents what the task does and may refer to external sources of information justifying and explaining the operations described by the task; Trigger: a message that may be passed to the task in order to start it even if its parent plan has not scheduled it to start; and finally Task Scheduling Constraints: logical constraints that prevent one task from starting before another task or set of tasks has been completed.

The PROforma processes can be represented diagrammatically as directed graphs in which nodes represent tasks and arcs represent scheduling constraints. A guideline itself contains a single root plan, which may be recursively divided into sub plans. A sample diagram modeled using PROforma is shown in Figure 2.

Expression Language

PROforma is a first-order logic formalism expressed in Backus-Naur Form (BNF) notation. In the BNF form the PROforma defines a set of proprietary operators and operations that can be used to sufficiently model medical decisions. It can be used to model complex medical decision and processes such as temporal reasoning.

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20 BNF is a formal notation to describe the syntax of a given language, such as temporal and argumentation logic.
21 Syntax specification is available at: http://www.acl.icnet.uk/.
Medical Concept Model

PROforma does not define an abstract medical concept model, instead it relies on the logic and queries embedded in each task for acquiring patient data needed in decision-making. In other words, PROforma requires a tight integration—customized database connection strings and queries—in order to be integrated with heterogeneous clinical information systems. Arezzo, the commercialized counterpart of PROforma, provides such integration solutions for major European EMR systems.

Tools

Arezzo Composer and Arezzo Performer are dedicated authoring and execution environments for working with PROforma-encoded guidelines. They are commercial products of the InferMed Ltd. The Advanced Computational Laboratory of Cancer Research also develops a similar counterpart, Tallis Composer, which is freely available for collaborative research use. The Tallis toolset is also an enactment engine, which can be used to publish package for making applications available over internet.

Automated Execution

The resulting computerized "enactable" clinical guideline representations can be tested and executed using a PROforma-compatible engine. PROforma also defines public operations that an external system may request the engine to perform, for instance an external system may invoke a public operation with patient information as inputs and receive action recommendations as outputs. The guideline representations (tasks and their properties) are stored in a database which allows the enactment engine to retrieve and execute.

Level of Sharing

Although it is possible to transfer the guideline representations from one enactment engine to another, the PROforma is simply not a language specification designed for guideline sharing. It does not make use of the standards for storage and interchange of structured information, such as XML and RDF, and it does not comply with any of the health information exchange standards, such as HL7. Developers of PROforma are currently working on XML semantics that can be used to represent tasks and data items defined in PROforma, in order to achieve certain level of interchangeability.

Applications

PROforma has been used to develop a wide range of prototype and routinely used clinical applications to provide advice on prescribing and aid in management of chronic disease conditions. InferMed Ltd, that commercializes the
PROforma technology under the brand name of Arezzo, has been a successful startup with many European clients.

Limitations

First, PROforma is not an representation language that is designed to enable guideline sharing. While PROforma and its commercial version Arezzo have been routinely used in a number of applications, they do not provide a sufficient platform and accompany toolsets for representing and disseminating guidelines. The PROforma model has many proprietary specifications of tasks and data items, which do not make use of any of the existing standards for structured data storage and exchange. In addition its guideline representations are stored in a relational database with proprietary schemas.

Second, the PROforma model does not have an abstract layer representing patient data elements and their properties, which in turn requires customized interfaces to be built in order to retrieve patient data for effective decision-making. The PROforma-based systems largely relies on rules embedded in properties of each task for data acquisition, for example the Enquiries task and the Actions task keep track of external sources and methods of data acquiring or manipulating, either by issuing SQL queries to a database system or raising the event to a person. This architecture requires tremendous effort in revising PROforma guideline representations in order to incorporate site-specific details.

4 Ontologies and Clinical Decision Support Systems

Based on the review of several representative ontologies and the in-depth analyses of GLIF3 and PROforma, this section summarize the ontology approach by conceptualizing common elements constituting a guideline representation, and outlining general steps for computerizing an evidence-based clinical practice guideline using formal ontologies.

4.1 Decomposing Clinical Practice Guidelines

While different ontology models take different design choices, their common characteristics collectively reveal the underlying structure of the descriptive guideline publications. In general, most clinical guidelines can be decomposed into the following seven major concepts:

1. **Triggering Criteria**: Initial screening to determine whether a patient should enter the guideline protocol. It provides general guidance on patient population or geographic region that the guideline can be applied to. It may also be relevant to its intended practice environments, such as children care providers or specialists of a certain type of disease;
2. **Information Flow**: An overall structure of a guideline, typically temporal sequences that connect various elements;

3. **Decisions**: Logic of evaluating criterion for making a medical decision;

4. **Actions**: Actions to be taken based on results of evaluating a decision criterion, typically treatment plans to be recommended;

5. **Exceptions**: Plans when statements specified in a guideline cannot be performed or are not valid under certain circumstances;

6. **Medical Terminologies, Data Structure, and Data Acquiring Methods**: How to map a statement such as “check the asthma severity” to computer-interpretable queries that typically lead to a database lookup;

7. **Relationships among Guidelines and Guideline Components**: A virtual construct that enables a guideline to contain other guidelines or a subset of another guideline. For example, an estimation of ten-year risk of fatal cardiovascular disease can be included in several chronic management guidelines.

### 4.2 Implementing Guideline using a Formal Guideline Ontology

Since many of the existing guideline ontologies share similar components, the procedures for representing an unstructured, descriptive guideline in computer-interpretable format can be generalized. We describe below a general four step process for implementing a computer-interpretable guideline using a formal guideline ontology. The resulting guideline representations can be then incorporated into Clinical Decision Support Systems to support medical decision-making.

1. **Knowledge Acquisition**: A conceptual level, preliminary flowchart is created by a panel of medical experts. This flowchart captures the basic elements and flow of information of a guideline, such as the one illustrated in Figure 3;

2. **Medical Terminology Mapping**: Based on the preliminary flowchart, a panel of medical experts and informaticians needs to determine medical terminologies that can be used to represent the narrative statements of medical concepts, for instance “diabetes diagnosis” should be translated into “250.” (ICD-9-CM is used here for illustration). Because a variety of controlled vocabularies are available, the panel needs to make a decision about which vocabulary to use if ambiguity exists. In addition, the medical concepts in a guideline statement may contain composite elements. Such concepts must be decomposed to a level that matches the structure in which these concepts are stored in EMRs. For example, a short-acting beta-agonist treatment contains a class of drugs such as Albuterol, Proventil, and Ventolin; and a Lipid Profile test may
include individual tests of HDL, LDL, Triglycerides, and Total Cholesterol. There exist other considerations that may further complicate the situation, for instance the panel needs to determine whether “Albuterol” represents a generic drug name, or a name of a drug class, or an ingredient contained in a drug formula.
<table>
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<tr>
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<th>Data Item</th>
<th>Data Item Code</th>
<th>Logical Pseudo Code</th>
<th>Exception</th>
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<td>○ Diagnosis</td>
<td>Procedure</td>
<td>○ Other</td>
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<tr>
<td>Tested testosterone within last year?</td>
<td>○ Medication</td>
<td>○ Diagnosis</td>
<td>Procedure</td>
<td>○ Other</td>
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<td>○ Diagnosis</td>
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<td>○ Other</td>
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<td>Bone density done with 1 year?</td>
<td>○ Medication</td>
<td>○ Diagnosis</td>
<td>Procedure</td>
<td>○ Other</td>
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<tr>
<td>On ≥ 2 mg/day PREDNISONE or an equivalent?</td>
<td>○ Medication</td>
<td>○ Diagnosis</td>
<td>Procedure</td>
<td>○ Other</td>
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<tr>
<td>On Biphosphonate?</td>
<td>○ Medication</td>
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<td>Bone density &lt; -2.5?</td>
<td>○ Medication</td>
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<td>Procedure</td>
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<td>Had a spine or hip fracture?</td>
<td>○ Medication</td>
<td>○ Diagnosis</td>
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<tr>
<td>On Estrogen?</td>
<td>○ Medication</td>
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<td>Procedure</td>
<td>○ Other</td>
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Fig. 4. A Sample Worksheet for Medical Terminology Mapping
3. **Guideline Encoding**: This step is performed by a trained modeler who is familiar with the specifications of the ontology being used. The modeler uses the associated guideline encoding tool which typically supports visualized guideline encoding, to computerize the conceptual flowchart created in the knowledge acquisition step. More specifically, the modeler draws a set of defined shapes to represent various entities and connects them with unilateral lines to represent temporal sequences of execution. Next the modeler defines the vocabulary choices and advanced rules determined in the medical terminology mapping step. The modeler finally specifies data elements that are needed for executing the current guideline.

Although this step requires significant amount of effort by a modeler, it is one-time investment and the resulting representation is straightforward and it hides most of the details at various layers of abstraction. This representation, essentially a flowchart that looks no different from the conceptual flowchart created in step 1, can be directly edited by clinicians for customization or incremental updates (such as change of a threshold value based on newly published evidence). Figure 5 shows an example of the resulting visual diagram, where the highlighted path illustrates a possible decision-making pathway.

4. **Guideline Execution**: Depending on the nature of the tool, the encoding converts the computerized guideline representations into a programming
language and compiles it into executable which can be used by the system in which the guideline is implemented. The Guideline Execution Engine (GLEE), for example, is the tool for executing the guidelines encoded in the GLIF3 format.

5 Conclusion

This chapter introduces the concept of guideline representation ontology, which is a specification of conceptualizations that constitutes evidence-based clinical practice guidelines. The main purpose of introducing the concept of ontology into knowledge representation is to enable knowledge sharing and reuse. Over the past several years, many ontology models for representing clinical practice guidelines have been developed, and become more expressive and powerful over time. However, there are several outstanding issues that must be resolved before any specific ontology can become widely adopted. The most critical prerequisite for wider acceptance of a guideline ontology is that it should be comprehensive enough to represent complex guidelines. Second, the guideline ontology should be simple enough to represent guidelines with a minimal set of constructs. Furthermore, since medical professionals are integral members of the guideline development and revision process, the ontology and related tools should be developed so clinicians with no advanced programming knowledge can revise and customize the guideline representations. To achieve this goal, the model must be accompanied by user-friendly tools for modification, and execution.

This chapter reviews several representative ontologies, and presents in-depth analyses of two popular models: GLIF (Guideline Interchange Format) and PROforma. These ontology models have advanced the state of knowledge on how to represent clinical practice guidelines in computer-interpretable format; however, they all share certain limitations that have prevented their widespread use. First, most of these models are experimental ontologies that lack proven validity and effectiveness in practice. Second, many of the existing ontology models do not support automated guideline execution: while these representations of clinical practice guidelines are stored in a structured, computer-interpretable format, they are not algorithms that may be programmed directly into CDSSs. Third, some of the existing models are specialized in certain disease areas, i.e. their knowledge domains may be too narrow to represent generic types of guidelines. On the other hand, more generalized ontology models are often too complex to be used by clinician users who have little or no advanced computer knowledge. Finally, software tools provided to support editing, visualizing, and executing guideline representations encoded in these ontologies are not user-friendly.

A second set of major considerations revolves around a guidelines ability to be exchanged without significant effort, both for the distributor and the receiver. Exchange of guidelines can be performed at execution level, i.e.,
computerized guideline representations can be directly shared across execution environments. For a receiver, adaptation of the guideline to the specific constrains of the implementation site, should require minimal redesign. To fulfill this requirement the model should provide an abstract layer that separates site-specifics from generic guideline representations. In addition to an ontology’s ability to represent complex logic and its ability to be distributed without significant modification, it should have enough flexibility so that it can be used for different purposes and allows for future expansions. Furthermore, it should support established medical terminologies and standards data exchange standards.

Currently, there are a significant number of solid guideline ontologies to choose from when developing Clinical Decision Support Systems. However, the field is still active and much progress can be expected in the coming years, both in the improvement of existing ontologies as well as the development of novel ontologies and methods for representing clinical knowledge and decisions in computerized clinical decision support systems.
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