Integrated Knowledge Management (IKM) Volume 5

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Table of Contents

List of Figures

List of Tables

Part I. Terminology Knowledge

Table of Contents

1. Terminology Knowledge

1.1. Introduction

For an introduction to Terminology Standards, please refer to Integrated Knowledge Management (IKM) Volume 2 - Background Section 1.5 Terminology Overview.

1.2. What is LOINC®?

Bodenreider et al. provide an overview of LOINC®:

Logical Observation Identifiers, Names, and Codes (LOINC®) is a clinical terminology for identifying health measurements, observations, and documents. LOINC® was initiated in 1994 by the Regenstrief Institute, a non-profit medical research organization associated with Indiana University. By 1994, many electronic systems were sending clinical information as discrete results using messaging standards such as Health Level Seven (HL7) or ASTM 1238 (American Society for Testing and Materials). Inside these messages, laboratories and clinical systems used local, idiosyncratic names and codes to identify which test was being reported. This practice was problematic for data exchange and aggregation because of the large resources it takes to map codes between every participating system.

To solve this problem, Regenstrief organized the LOINC® Committee to develop a common terminology for laboratory and clinical observations. Existing terminologies were not granular enough, focused on coding for billing rather than clinical results delivery, or did not fit with the messaging models being used. Because such a standard did not exist, the LOINC® Committee embarked on creating a terminology with [an] appropriate level of granularity for defining the names of observations used in laboratory and clinical information systems. Since its creation, LOINC® has continued to be developed and published by the Regenstrief Institute as a freely available global standard with a set of implementation tools. Today, LOINC® is used by a diverse global community that propels its continuous development.

LOINC's® primary role is to provide identifiers and names for observations. Here, observation [is used] as a generic term for health data represented in a particular way. In different domains, these might be called tests, variables, or data elements. Within and among health IT systems, observations are communicated with a structure that has two key structural elements. The first element identifies what the observation is, e.g., diastolic blood pressure, hematocrit, tobacco smoking status. The second element carries the result value of the observation, e.g., 80 (mmHg), 40 (%), or "current everyday smoker". When used together, these two elements carry the instance of a specific test result for a given patient. A common pairing is to use LOINC® as the standard code for the observation, and Systematized Nomenclature of Medicine Clinical Terms® (SNOMED CT®) as the standard code for the observation value, when needed. This approach is endorsed by the developers of both terminologies and fits their design purpose.

Some mistakenly believe that LOINC® is only for laboratory tests. It is true that the first release of LOINC® in May 1995 contained only terms for laboratory testing, but by December of 1996, LOINC® had already added about 1,500 clinical measurement terms (vital signs, ECG measures, etc). Now, more than 20 years and 60 releases later, LOINC® has grown significantly in other domains, including radiology, standardized survey instruments and patient-reported outcomes measures, clinical documents, nursing management data, and nursing assessments. The LOINC® Committee itself is now composed of three major composite committees: Laboratory, Clinical, and Radiology. [1]

1.2.1. LOINC® Current State

Regenstrief continues to update LOINC® and publish twice-yearly releases. New concepts are added to LOINC® based on submissions from end users. The current version contains more than 99,000 terms

covering the full scope of laboratory testing (chemistry, microbiology, molecular pathology, …etc.) and a broad range of clinical measurements (e.g., vital signs, ECG, patient-reported outcomes, …etc.). In addition to distributing the terminology, Regenstrief makes available at no cost a variety of supporting tools and resources, including the Regenstrief LOINC® Mapping Assistant (RELMA®) and online search application.

LOINC® uses a semantic data model containing six major and up to four minor attributes to create fully-specified names for concepts. The major attributes of the LOINC® name are:

1. Component (e.g., what is measured, evaluated, or observed)

2. Kind of property (e.g., mass, substance, catalytic activity)

3. Time aspect (e.g., 24-hour collection)

4. System type (e.g., context or specimen type within which the observation was made)

5. Type of scale (e.g., ordinal, nominal, narrative)

6. Type of method (e.g., procedure used to make the measurement or observation).

The atomic elements that make up each LOINC® term name are called “Parts” and are also assigned identifiers. The combination of attribute values produce term names that are [intended to be] detailed enough to distinguish among similar observations. Of the six attributes, only the method is optional and used only when necessary to distinguish among clinical important differences.

“A fully specified test result or clinical observation can be described formally with the following syntax: <Analyte/component>:<kind of property of observation or measurement>:<time aspect>:<system (sample)>:<scale>:-<method>.” [2]

Over time, LOINC® has not only grown in size, but also developed additional data structures and content around its main codes for individual observations. The LOINC® release contains a basic hierarchy that organizes LOINC® codes into a set of is-a relationships. LOINC® now has a detailed model for representing enumerated collections of observations, such as laboratory panels (complete blood count), assessment instruments (e.g., PHQ-9), data sets (National Trauma Data Standard), and forms (e.g., U.S. Standard Birth Certificate). This content is published in a special release artifact called the LOINC® Database, with the current version (August 2022) containing more than 99,000 terms. LOINC® also has a detailed model for connecting observation terms to structured answer lists. These answer lists can be defined by extension or intension and linked to observation terms with different types (e.g., example, preferred, normative). This content is published in the LOINC® Answer List File, with the current version (August 2022) containing links between 25,640 unique LOINC® terms and 4,341 unique answer lists composed of coded LOINC® Answers, and including mappings to other terminologies such as SNOMED CT® where they exist. LOINC® now also publishes the atomic elements (called Parts) that make up each LOINC® term name. The LOINC® Part File includes the Part identifiers and names, links between Parts and LOINC® terms, and mappings from LOINC® Parts to other terminologies such as SNOMED CT® and RxNorm where they exist.

1.2.2. LOINC® Collaboration

The following *italicized excerpts* provide an overview of Regenstrief’s relationship with the health community in the development of LOINC®. Non italicized text reflects updates and discussion to reflect the current state.

Regenstrief is committed to working with developers of health data standards that are complementary to LOINC®, including syntax standards for data exchange and other terminology standards. Regenstrief and

HL7 have a long-standing collaboration; a few joint work highlights include clinical genomics guides, claims attachments specifications, and approaches for representing vocabulary standards in Fast Healthcare Interoperability Resources (FHIR) terminology services. Regenstrief Institute made core LOINC® content available via a FHIR API as part of its normal release process beginning Summer 2018.

In April 2022, a LOINC® Terminology Service using the FHIR Standard was launched with an API that provides a means for users to access LOINC® content across multiple versions programmatically.]

Regenstrief and the Institute of Electrical and Electronics Engineers (IEEE) Standards Association, developer of the 11073™ standards, are collaborating to enhance the interoperability of traditional medical devices and personal health devices. Regenstrief is an active member of the Health Standards Collaborative (HSC) which provides an executive forum for senior leadership of the U.S. healthcare standards development community to improve interoperability. In 2017, Regenstrief worked with the In Vitro Diagnostic (IVD) Industry Connectivity Consortium (IICC) on a specification for publishing vendor IVD tests associated with a set of LOINC® codes that identify the distinct observations produced by the test.

In the context of the specifications of the U.S. Meaningful Use incentive program, LOINC® is the primary choice for specifying attributes, and SNOMED CT® the system of use for the relevant attribute values. In other words, LOINC® is used to specify the question (e.g., 29308-4: "what is the diagnosis?"), and SNOMED CT® to specify the answer (e.g., 3723001: "Arthritis"). Adoption of this principle by both the Regenstrief Institute and SNOMED International has formed the basis for the cooperation agreement. In 2013, Regenstrief and SNOMED International formed a long-term collaborative relationship to link the rich clinical semantics of SNOMED CT® to LOINC®, which provides extensive coverage of laboratory tests and clinical measurements. [1]

While the initial partnership and memorandum of understanding signed between SNOMED CT® and LOINC® developers paved the way for development teams to facilitate interoperability and minimize duplication of effort, the collaborative relationship did not accomplish a complete integration of the two disparate terminologies. Further integration has been proposed to leverage SNOMED CT®'s model for the representation of LOINC® building blocks and for a more consistent representation of clinical and laboratory observations in SNOMED CT®. Furthermore, the use of description logics for the representation of LOINC® was not accomplished under this initial partnership in 2013 and only SNOMED CT® currently uses this formalism. LOINC® still uses its distinct formalisms and tools for its representation, has its own release cycles and versioning mechanisms, which makes seamless integration with SNOMED CT® non trivial, if possible at all.

1.3. What is SNOMED CT®?

Bodenreider et al. provide an overview of SNOMED International:

Since the inception of the Systematized Nomenclature of Pathology (SNOP) in 1965, the various versions of SNOMED have developed both in terms of content and underlying representation. Development of content is clearly illustrated by the number of elements in the various systems. SNOP comprised "about 15,000 distinct medical objects, processes, and concepts". It developed further into SNOMED-2, and later SNOMED International, which contained 150,000 concepts in the mid-1990s. Its successor, SNOMED Reference Terminology (SNOMED RT), contained over 120,000 active concepts. The initial version of SNOMED CT®, the merger of SNOMED RT® and the UK-based Clinical Terms Version 3, released January 2002, consisted of 278,000 active concepts, a number that has grown to 350,000+ in the January 2022 release of SNOMED CT®. The representation has gone through phases of increasing formal rigor. The initial SNOP and SNOMED versions were multi-axial systems that enabled post-coordination. Whereas SNOP started as a 4-axis system, SNOMED International had expanded to using 12 axes: anatomy (topography), morphology (pathologic structure), normal and abnormal functions, symptoms and signs of disease, chemicals, drugs, enzymes and other body proteins, living organisms, physical agents, spatial relationships, occupations, social contexts, diseases/diagnoses and procedures. SNOMED RT® abandoned

the use of self-standing axes that could be combined into composite codes in favor of a description logic formalism called Ontylog, based on the Knowledge Representation System Specification (KRSS) syntax and the K-REP system. Following contemporary naming conventions for description logics, the set of constructors used corresponds to the ## ++ language. SNOMED CT® has continued to use this description logic as its underlying representation. The evolution of the representation of "arthritis" through the history of SNOMED provides an illustration of editorial changes over time, with examples from SNOMED-2, SNOMED International, and the current version of SNOMED CT®. [1]

1.3.1. SNOMED CT® Current State

Regarding the current state, Bodenreider, et al., go on to say:

Since the first release of SNOMED CT® in January 2003, updated versions have been released twice a year. Maintenance can lead to a decrease of the number of elements, e.g., in January 2010 when, among others, the veterinary content was removed from the International Release. [1]

The July 2022 release contains 356,817 active concepts, 1,202,379 active relationships and 1,286,456 active descriptions. The largest categories of concepts in SNOMED CT® are disorders (23%), procedures (16%), body structures (11%), clinical findings other than disorders (10%), and organisms (9%). In SNOMED CT® parlance, descriptions are labels that describe the concepts, not textual definitions of the concept, of which SNOMED CT® contains 9762.

A significant design criterion for SNOMED CT® is to keep concept expressions simple enough to be broadly usable by clinicians, while maintaining faithful representation of concept meaning. Validity of concept expressions is determined by adherence to the concept model underlying SNOMED CT®. This concept model specifies which types of relationship are allowed for which concepts, and what the allowed values are. For example, the concept model specifies that "Method" is an allowed attribute relationship for "Procedure" concepts, for which the value should be a type of "Action". The January 2018 release uses 82 relationship types, almost twice the number of the initial 42 relationship types. Since July 2017, the concept model is available in machine-readable form, and distributed as separate tables which are part of the semi-annual releases. Other tables provide mappings to several versions of the International Classification of Diseases (ICD9-CM, ICD-10 and ICD-O). The current release format, called Release Format 2 (RF2), supports versioning, providing access to any previous release of SNOMED CT®.

While SNOMED CT® has made much progress in their use of description logics, and have also provided a tool on github, snomed-owl-toolkit, to facilitate the conversion and classification process, the official distribution of OWL refsets has yet to be seen. It seems one reason is the lack of current clinical systems to utilize them at this time. [3-4]

1.3.2. SNOMED CT® Collaborations

Here's an excerpt of what Bodreider et al. have to say about Collaboration Initiatives:

SNOMED CT® is not developing in isolation, but increasingly collaborating and harmonizing with other relevant standards in the area of structured and standardized storage and exchange of biomedical data. This includes mapping, as well as binding of information model and terminology. Mappings are maintained between SNOMED CT® and a number of terminology systems. These include the World Health Organization (WHO) classifications (e.g., versions ICD-10 and ICD-O of the International Classification of Diseases), as well as the International Classification of Primary Care (ICPC-2), the International Classification for Nursing Practice (ICNP), and LOINC®. The latter is especially important in the context of the specifications of the U.S. Meaningful Use incentive program, in which LOINC® is the primary choice for specifying attributes, and SNOMED CT® the system of use for the relevant attribute values. In other words, LOINC® is used to specify the question (e.g., 29308-4: "what is the diagnosis?"), and SNOMED

CT® to specify the answer (e.g., 3723001: "Arthritis"). Adoption of this principle by both the Regenstrief Institute and SNOMED International has formed the basis for a cooperation agreement in 2013.

SNOMED CT® also has collaborations for specific domains. In the context of rare diseases, collaboration with Orphanet leads to harmonization of content between SNOMED CT® and ORDO, the Orphanet ontology of rare diseases. Medical device terminology is addressed in collaboration with the Global Medical Device Nomenclature Agency (GMDNA). Finally, Kaiser Permanente's Convergent Medical Terminology (CMT) provides concepts and descriptions to be considered for inclusion. Moreover, SNOMED CT® forms the backbone for the development of national extensions by member countries of SNOMED International. National extensions typically contain concepts that are important in a given country, but not in scope for the international release of SNOMED CT®. Other extensions, such as the veterinary extension, contain content specific to a given community of practice.[1]

1.4. What is RxNorm?

Here's an excerpt of Bodenreider et al. overview of RxNorm:

At the dawn of the twenty-first century, there was no standard terminology for drugs in the U.S.. While many companies provide information about drugs for use in clinical information systems (e.g., to support clinical decision), each drug knowledge base defines its own codes and names for medications, making it difficult to exchange information across clinical information systems and to retrieve information from different systems. For example, the same transdermal patch delivering 0.583 milligrams of nicotine per hour for 24 hours (e.g., to help with smoking cessation) is referred to with the following codes and names in three of the major drug knowledge bases: • 2707 nicotine 14 mg/24 hr transdermal film, extended release • 102712 Nicotine 14 MG/24 HR Transdermal Patch, Extended Release • 016426 NICOTINE 14 mg/24 hour T R A N S D E R M P A T C H , TRANSDERMAL 24 HOURS In addition to capitalization differences, there is a lack of standardization in naming dose forms (transdermal film vs. transdermal patch) and units (24 hr vs. 24 hour), making it difficult to parse names from multiple systems. RxNorm was created to address the lack of standardization in drug names, and to make drug terminologies interoperable by integrating them into a reference system. Since the 1990s, the National Library of Medicine (NLM) has released the Unified Medical Language System (UMLS), a terminology integration system in which names and codes from all major biomedical terminologies are integrated, and equivalent terms across vocabularies are identified. RxNorm can be thought of as a specialized version of the UMLS. While both UMLS and RxNorm are built upon existing vocabularies, one major difference between the two is that UMLS generally does not create names for biomedical entities. In contrast, RxNorm creates a "normal form" for every drug entity it integrates. In RxNorm parlance, normal forms are standardized terms for drug entities. For example, the normal form for the nicotine patch discussed above is "24 HR Nicotine 0.583 MG/HR Transdermal System", to which RxNorm permanently assigns the concept unique identifier 198029. Unlike the UMLS, RxNorm also defines a rich network of named relationships among the various types of drug entities it integrates (e.g., ingredient, brand name, generic drug product, branded drug product). The main use cases RxNorm was designed to support include electronic prescribing, drug information exchange, and mapping across drug vocabularies (e.g., for medication reconciliation purposes). Standard names and codes for drugs were also expected to facilitate the development of standard clinical decision support rules involving medications. RxNorm started in 2002. It was first released through the UMLS and has been published as an independent terminology with monthly releases since November 2004, and weekly updates since 2008 to reflect drugs recently marketed in the U.S. market. The number of sources integrated in RxNorm has grown from 5 to 13.[1]

1.4.1. RxNorm Current State

Bodenreider et al. go on to talk about the current state:

Sources. RxNorm currently integrates terminology information from most drug knowledge base vendors (e.g., First DataBank, Multum, Micromedex, Gold Standard), as well as the drug component of stan-

dard terminologies (e.g., SNOMED CT®, MeSH). RxNorm also integrates sources from several public entities.More recently, RxNorm has also integrated international drug resources, such as the Anatomical Therapeutic Chemical (ATC) Classification System and DrugBank, a drug resource used in many research projects.

Organization. The RxNorm drug model distinguishes between generic and branded drug entities and identifies three major definitional elements for drug products, namely ingredient, strength, and dose form, along with two additional elements, quantity factor and qualitative distinction. The major types of drug entities include ingredient (e.g., Azithromycin), brand name (e.g., Zithromax), clinical drug (e.g., Azithromycin 250 MG Oral Tablet), and branded drug (e.g., Zithromax 250 MG Oral Tablet). Generic and branded packs are collections of clinical and branded drugs, respectively (e.g., Z-PAK, a branded pack of 6 tablets of 250 milligrams of azithromycin). While drugs are sold mostly pre-packaged in some countries (e.g., individual tablets in blister packs), packs are available for a minority of drugs in the U.S. In addition to the six major drug entities, RxNorm provides entities for navigational purposes. Clinical and branded drug components associate ingredient (or brand name) and strength information, and clinical and branded dose forms associate ingredient (or brand name) and dose form information.

The various types of drug entities in RxNorm are organized into a graph that can be easily traversed, enabling users to navigate among types of entities (e.g., to find the branded drugs associated with a given ingredient). While its main organization principles have remained centered on the ingredient-strength-dose form triad, RxNorm has added definitional features to accommodate distinctions, such as duration for extended release forms and transdermal systems (e.g., the quantity factor "24 HR" in "24 HR Nicotine 0.583 MG/HR Transdermal System") and size of unit of presentation for injectable medications (e.g., the quantity factor "40 ML" in "40 ML Ciprofloxacin 10 MG/ML Injection"), as well as qualitative elements for specific drugs (e.g., the qualitative distinction "Sugar-Free" in "Sugar-Free Cholestyramine Resin 4000 MG Powder for Oral Suspension"). A drug product in RxNorm is fully defined by its set of ingredient, strength, dose form, quantity factor, and qualitative distinction values. Types of ingredients include multi-ingredients (e.g., Sulfamethoxazole / Trimethoprim) and "precise ingredients" (e.g., Atorvastatin calcium, Morphine Sulfate), generally denoting, salts, esters, and complexes of base substances. As illustrated in the examples above, RxNorm normal forms reflect the definitional features of drug entities. Additionally, RxNorm explicitly links drug entities to these features, which supports efficient processing. For example, the generic nicotine patch "24 HR Nicotine 0.583 MG/HR Transdermal System" is linked to its ingredient (Nicotine), strength (0.583 MG/HR), dose form (Transdermal System), and quantity factor ("24 HR").

The scope of RxNorm is different from that of drug knowledge bases. RxNorm focuses on drug names and codes. In other words, clinical information (e.g., indications, drug classes, and drug-drug interactions) and administrative information (e.g., drug pricing) are out of scope for RxNorm. Although it integrates international sources (e.g., ATC, DrugBank), RxNorm focuses on drug products marketed in the U.S. Finally, non-therapeutic radiopharmaceuticals, bulk powders, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm.[1]

The September 2022 edition of RxNorm includes 13856 (base) ingredients, 5065 brand names, 17226 semantic clinical drugs, 9424 semantic branded drugs, 474 generic packs, and 543 branded backs.

With each monthly update, the RxNorm content is kept current and in sync with drugs available on the U.S. market, i.e., new drug products are added and drug products no longer available are retired. RxNorm identifiers are never reused and can be safely used as permanent identifiers for drugs in clinical data warehouses and prescription datasets. However, any given release of RxNorm only contains detailed information about active drug products in that release.

In 2019 Medication - Reference Terminology (MED-RT) replaced National Drug File - Reference Terminology (NDF-RT). [5] RxNorm is available as a resource in the HL7 FHIR website. While it is currently in Standard for Trial Use (STU), it has been advancing through the HL7 Ballot Levels to expose the RxNorm content as medication resources. [6]

1.4.2. RxNorm Collaborations

In regards to RxNorm collaborations, Bodenreider, et al. has this to say:

In the development of RxNorm content, NLM has worked in close collaboration with the vendors of drug knowledge bases, with federal partners, and with representatives of the pharmacy services industry represented by the National Council for Prescription Drug Program (NCPDP). Similarly, the development of RxNav and the RxNorm API have greatly benefited from the feedback provided by their user community. For the past five years, NLM has held an annual DailyMed/RxNorm Jamboree Workshop to bring together the RxNorm stakeholders. To extend the usefulness of RxNorm despite its limited scope, NLM has also initiated partnerships with providers of clinical information that can be linked to RxNorm. For example, NLM has developed companion APIs to link RxNorm drugs to various drug classification systems and to publicly available sources of drug-drug interaction information. Drug classes for RxNorm drugs can also be explored through the RxClass application.

The table below is a comparison of terminologies on how well they meet Cimino's Desiderata. [7] The Desiderata is a list of attributes needed for a standard terminology to meet the needs of its users. SNOMED CT® is the only terminology that meets all the requirements as described by Cimino. However, as noted above, SNOMED CT® has proprietary elements that limits its usefulness for interoperability.

Table 1.1. Met Criteria of LOINC®, SNOMED CT® and RxNorm to Cimino's Desiderata

Tenant	LOINC®	SNOMED CT®	RxNorm
Concept Orientation	None	Complete	Complete
Concept Permanence	Complete	Complete	Partial
Non-Semantic Concept Identifier	Complete	Complete	Complete
Polyhierarchical	None	Complete	Complete
Formal Definitions	None	Complete	Partial
Classification	None	Complete	Complete
Multiple Granularities	None	Complete	Complete
Multiple Consistent Views	None	Complete	Complete
Representation of Context	None	Complete	Complete

1.5. Terminology Principles and Best Practices

This section contains an overview of principles and best practices for terminology design and representation.

1.5.1. Understandable, Reproducible, Useful (URU)

There are core evolutionary design principles called "Understandable, Reproducible, and Useful," upon which SNOMED CT® development is still based. [8-9] These criteria describe an approach for improving data quality and increasing data integrity and agility:

- *Understandable: the content can be processed by health IT systems and understood by most healthcare providers without reference to private or inaccessible information;*
- *Reproducible: multiple users or systems apply the data to the same situations and source data with an equivalent result; and*
- *Useful: data is fit-for-purpose – it has practical value for data analysis in support of health information exchange, research, and public health that requires information aggregated across health IT systems.*

1.5.2. The Desiderata for Controlled Medical Vocabularies in the 21st Century

Jim Cimino developed a series of tenants that are essential for a strong terminology model [7]:

1. **Concept Orientation** – terms should be exact in meaning and non-ambiguous
2. **Concept Permanence** – once a concept is created, its meaning will never be changed
3. **Non-Semantic Concept Identifier** – every concept must have a unique identifier
4. **Polyhierarchy** – hierarchical arrangements are necessary in medical vocabularies. “There seems to be almost universal agreement that controlled medical vocabularies should have hierarchical arrangements… There is some disagreement, however, as to whether concepts should be classified according to a single taxonomy (strict hierarchy) or if multiple classifications (polyhierarchy) can be allowed. Most available standard vocabularies are strict hierarchies.”
5. **Formal Definitions** – “These definitions are expressed as some collection of relationships to other concepts in the vocabulary”
6. **Every Concept has a Classification** - reject “not elsewhere classified”
7. **Multiple Granularities**
8. **Multiple Consistent Views** – fine-grained concepts should be able to be collapsed into more coarse-grained concepts and appear as synonyms; and
9. **Representation of Context** - Beyond medical concepts: representing context.

1.5.3. Knowledge Representation and Description Logic

A report in the 2016 Yearbook of Medical Informatics defines terminology as “a system of concepts with assigned identifiers and human language terms, typically involving some kind of semantic hierarchy. Some systems may support the assignment of multiple terms, or synonyms, to a given concept; these may include terms in multiple natural languages, such as English or Dutch.” [10] This definition implies that knowledge representation for a terminology system may not always be based on a strict defining hierarchy. The advantage, or disadvantage, of such an approach is that the terminology, such as LOINC® for instance, might appear to be rather intuitive and human-readable and comprehensible. However, when delving into complex use cases, a lack of formal defining structure may reveal that it is difficult to understand the precise meaning of the terminological representations and that use of a system such as LOINC® may differ widely amongst humans. Further exacerbating potential variability is the heterogeneous behavior of tools implemented to reason with terminological structures. [11]

The field of Knowledge Representation and “Description Logics” was developed out of the attempt to formally define “intuitive representations” with a formal semantics to establish a common ground for human and tool interoperability. Knowledge representation involves the design of formalisms for expressing knowledge about a particular domain and focuses on representing and characterizing classes of objects and relationships between them.

An ideal state terminology that relies on description logics may invoke more formal semantic relationships between and among concepts. Use of a Description Logics reasoner can help in overcoming important drawbacks of multi-axial systems and other non-standard, distinct formalisms: (1) the capability of detecting semantic equivalence of syntactically different expressions, and (2) the automated classification of concepts in a hierarchy.

1.5.4. SNOMED CT® Design Criteria

Bodenreider et al. provide an overview of SNOMED Design Criteria:

The representation of SNOMED has gone through phases of increasing formal rigor. The initial SNOP and SNOMED versions were multi-axial systems that enabled post-coordination. Whereas SNOP started as a 4-axis system, SNOMED International had expanded to using 12 axes. SNOMED RT® abandoned the use of self-standing axes that could be combined into composite codes in favor of a description logic formalism called Ontylog, based on the Knowledge Representation System Specification (KRSS) syntax and the K-REP system. Following contemporary naming conventions for description logics, the set of constructors used corresponds to the EL ++ language. SNOMED CT® has continued to use this description logic as its underlying representation.

A significant design criterion for SNOMED is to keep concept expressions simple enough to be broadly usable by clinicians, while maintaining faithful representation of concept meaning. Validity of concept expressions is determined by adherence to the concept model underlying SNOMED CT®. This concept model specifies which types of relationship are allowed for which concepts, and what the allowed values are. For example, the concept model specifies that "Method" is an allowed attribute relationship for "Procedure" concepts, for which the value should be a type of "Action". The January 2018 release uses 82 relationship types, almost twice the number of the initial 42 relationship types. Since July 2017, the concept model is available in machine-readable form, and distributed as separate tables which are part of the semi-annual releases. Other tables provide mappings to several versions of the International Classification of Diseases (ICD-9-CM, ICD-10 and ICD-O). The current release format, called Release Format 2 (RF2), supports versioning, providing access to any previous release of SNOMED CT®. [1]

While SNOMED CT® has committed to an application of formal methods and rigor to its knowledge representation, others have explicitly rejected the value of description logic and chose not to provide a defining taxonomy or fully define LOINC® parts.

1.6. Comparing LOINC®, SNOMED CT® and RxNorm to Cimino's Desiderata

Despite the guiding principles for terminology design and representation summarized above, "LOINC® does not fulfill the definition of a computable medical terminology as articulated by Cimino et al., that being one based in concept orientation, concept definition, and polyhierarchy. These characteristics enable the logical inference between concepts, parts, and part elements." [12] LOINC® is a well-maintained terminology – there is a deprecation process and has concept permanence where codes aren't reused – but they do not establish the basic parameters of hierarchy and polyhierarchy. And, they are violating the tenants of Cimino's Desiderata.

Table 1.2. Correspondence of LOINC® to Cimino's Desiderata

Tenant	**LOINC®**
Concept Orientation	No
Concept Permanence	Yes
Non-Semantic Concept Identifier	Yes

Polyhierarchy	No
Formal Definitions	No
Classification	No – they have a miscellaneous code
Multiple Granularities	No
Multiple Consistent Views	No
Representation of Context	No, but they have Narrative Summary

1.6.1. Comparison of SNOMED CT® to Cimino's Desiderata

SNOMED CT® is the terminology of our current awareness most closely aligns with the Desiderata. As stated elsewhere, it uses Description Logics for computability and facilitates the use of reasoners to determine equivalence among various syntactic representations. The primary downsides are 1). Some proprietary concepts and 2). Lengthy concept submissions process for consideration into either the National or International editions. This lack of agility, efficiency and speed is apparent in crisis situations such as COVID-19 pandemic. Otherwise, it has proven to be robust and has a large global community to assist with its development and vetting.

Table 1.3. Correspondence of SNOMED CT® to Cimino's Desiderata

Tenant	**SNOMED CT®**
Concept Orientation	Yes
Concept Permanence	Yes
Non-Semantic Concept Identifier	Yes
Polyhierarchy	Yes
Formal Definitions	Yes
Classification	Yes
Multiple Granularities	Yes
Multiple Consistent Views	Yes
Representation of Context	Yes

1.6.2. Comparison of RxNorm to Cimino's Desiderata

While RxNorm meets most of the Desiderata's requirements, there are a few that are not met. Of particular importance is the lack of Description Logics. Use of a Description Logics reasoner can help in overcoming important drawbacks of multi-axial systems: (1) the capability of detecting semantic equivalence of syntactically different expressions, and (2) the automated classification of concepts in a hierarchy. RxNorm has another issue of not being a global standard as its development and main use is in the U.S. where it is a nationally recognized standard, i.e. Meaningful Use.

However, recent work by Bona et al. have been developing a Drug Ontology product (DrOn), based on RxNorm and Chemical Entities of Biological Interest Ontology, which is a modular and extensible ontology of drug products, their ingredients and biological activity to enable comparative effectiveness and allow researchers to query National Drug Codes (NDCs) in multiple ways. Bone et al. go on to say the following:

We have implemented a full accounting of national drug codes and RxNorm unique concept identifiers as information content entities, and of the processes involved in managing their creation and changes. This includes an OWL file that implements and defines the classes necessary to model these entities. A

separate file contains an instance-level prototype in OWL that demonstrates the feasibility of this approach to representing NDCs and the Concept Unique Identifiers (RxCUIs) and the processes of managing them by retrieving and representing several individual NDCs, both active and inactive, and the RxCUIs to which they are connected. We also demonstrate how historic information about these identifiers in DrOn can be easily retrieved using a simple SPARQL Protocol and RDF Query Language (SPARQL).[13]

This development may have a significant impact on improving knowledge management as well as the ability to utilize Description Logics reasoners with its attendant benefits.

Table 1.4. Correspondence of RxNorm to Cimino's Desiderata

Tenant	**RxNorm**
Concept Orientation	Yes
Concept Permanence	No – remapping, changing atoms, splitting, etc.
Non-Semantic Concept Identifier	Yes
Polyhierarchy	Yes
Formal Definitions	No – [Ingredients] [Strength] [Dose] enough?
Classification	Yes
Multiple Granularities	Yes
Multiple Consistent Views	Yes
Representation of Context	Yes

1.7. Current Opportunities for SNOMED CT®, LOINC® and RxNorm to Integrate, Enhance and Extend

1.7.1. SNOMED CT® Existing Limitations

1.7.1.1. Licensing Conditions

There are also licensing conditions to SNOMED CT® that historically prevented its use as a common format for LOINC®. [14] This issue needs to be addressed for building on SNOMED CT®'s foundation. Nonetheless, SNOMED CT®'s commitment to develop and expand their use of description logics formalism as called out by Tinkar efforts as well as their alignment with the Desiderata as described by Cimino, et at, is a step in the right direction.

1.7.1.2. Submission Process Time

While SNOMED CT® has a process for handling new concept requests and submissions, it is lengthy and not amenable to rapidly changing conditions as seen with COVID-19. While workarounds can be done, what is needed is a formal, standardized, and agile process to accommodate quickly changing conditions/situations. The ability to share and aggregate data nationally, if not internationally, is paramount.

1.7.1.3. Compositional Complexity

While SNOMED CT® uses explicit, elaborate axioms to clarify meaning, its complex representation (compositional grammar) limits its broad adoption. [15] The learning curve to appropriately learn, author, and represent concepts using SNOMED CT®'s compositional grammar (for post-coordinated expressions) and

constraint language is steep, resulting in few who want to spend the resources to learn. In addition, even for those who learn it, it takes substantial experience to develop the expertise to understand and demonstrate concept redundancy in a consistent and correct manner.

1.7.1.4. Inconsistent Representation

There are multiple ways to represent SNOMED CT® concepts, leading to inconsistent representation (i.e., lack of equivalence), ambiguity, and patient harm from low data quality. SNOMED CT® is still up for constant refinement especially for improving and standardizing concept representation, which makes it difficult for the user to determine equivalence, both within and across terminologies.

1.7.1.5. Interpretive Comments

Interpretive comments are meant to enrich measurement results. One specific example is a statement of measurement uncertainty, which is required by some metrological guidelines. Measurement uncertainty is invaluable in the correct interpretation of measurement results. [15] Because interpretive comments can be of crucial importance in patient care, it is critical to expand SNOMED CT® to thoroughly capture these concepts.

1.7.2. LOINC® Existing Limitations

1.7.2.1. Inconsistent Selection of Codes for the Same Test

Without concepts of polyhierarchy, concept orientation, and concept definition, there is additional pressure on technicians and other stakeholders to correctly specify the correct LOINC® code: “When the terminology model is ultimately weak, it forces more onto the [statement] model”. [15] “A challenge that remains to be solved is the binding of statement model and terminology. There is often no clear demarcation between what is represented in the statement model and what is represented in the terminology.” [9]

Consequently, laboratory technicians may select a LOINC® code with an incorrect part (i.e., the incorrect specimen or analyte) due to LOINC®’s multiaxial hierarchy, resulting in difficulties for data aggregation and understanding across both different technicians and institution. [12] It has been reported that choosing different ‘properties’ (i.e., parts) was the most frequent reason that different coding choices were made. [16] In a “study about correctness of LOINC® mapping, choosing different ‘Method’, ‘Scale’ and ‘Property’ attributes was the most common reason for different coding choices among three large institutions. For example, in the ‘Method’ axis, some institutions usually use a code that specifies the method (when available), whereas other institutions always choose terms that are “methodless”. Another example, is that in the ‘Scale/Property’ axes, LOINC® uses two distinct styles (Prid:Nar VS. Prid:Nom) for reporting the interpretation of laboratory tests (e.g. CFTR gene mutation analysis). The Narrative (Nar) scale is for free text results (sentences, paragraphs, sections), whereas the Nominal (Nom) scale is used for representing coded values, as when selecting an organism found on culture from a coded list of bacteria. The differences between these types are often subtle and require understanding the reporting system. Steindel et al. also concluded that for some purposes, such as finding any code that could be used to indicate the presence of a particular disease, rolling up LOINC® codes and ignoring some LOINC® axes (e.g. method, scale, or property) can be beneficial.” [16]

There is not much management in terms of education in what codes are used for, and medical technicians often do not have the LOINC® level of knowledge for encoding that is necessarily expected. [17] The results in the following example offer insight into how different codes may be selected for the same test from different laboratories.

Case Study 1: Cardiac Marker and Coagulation Laboratory Proficiency Tests [12]

Depending on the lab, technicians may choose different LOINC® codes for the same test. The College of American Pathologists (CAP) surveyed 90 lab participants on “practice setting, instrument(s) and test

method(s), and LOINC® code selection and usage in the laboratory and electronic health records" for 10 commonly ordered tests. 19.6% of codes reported were incorrect, with the highest error rates "observed in the property (27 of 275, 9.8%), system (27 of 275, 9.8%), and component (22 of 275, 8.0%) LOINC® axes. Errors in LOINC® code selection included selection of the incorrect component (e.g., activated clotting time instead of activated partial thromboplastin time); selection of panels that can never be used to obtain an individual analyte (e.g., prothrombin time panel instead of international normalized ratio); and selection of an incorrect specimen type."

Figure 1.1. Breakdown of LOINC® Codes Provided by Each Laboratory

Test	LOINC	Component	Property	Time Aspect	System	Scale	Method	Frequency
APTT	12185-5[a]	Coagulation surface induced	Time	Pt	Bld^Control[a]	Qn	Coag	1
	12345-1[a]							1
	14979-9	Coagulation surface induced	Time	Pt	PPP	Qn	Coag	32
	3173-2[a]	Coagulation surface induced	Time	Pt	Bld[a]	Qn	Coag	6
	3184-9[a]	Activated clotting time[a]	Time	Pt	Bld[a]	Qn	Coag	1
PT	34528-0[a]	PT panel[a]	—[a]	Pt	PPP	Qn	Coag	3
	5902-2	Coagulation tissue factor induced	Time	Pt	PPP	Qn	Coag	31
	5964-2[a]	Coagulation tissue factor induced	Time	Pt	Bld[a]	Qn	Coag	4
	5934-2[a]							1
INR	34528-0[a]	PT panel[a]	—[a]	Pt	PPP	Qn	Coag	1
	34714-6[a]	Coagulation tissue factor induced.INR	RelTime	Pt	Bld[a]	Qn	Coag	3
	38875-1[a]	Coagulation tissue factor induced.INR	RelTime	Pt	PPP/Bld[a]	Qn	Coag	1
	5902-2[a]	Coagulation tissue factor induced[a]	Time[a]	Pt	PPP	Qn	Coag	3
	5964-2[a]	Coagulation tissue factor induced[a]	Time[a]	Pt	Bld[a]	Qn	Coag	1
	6301-6	Coagulation tissue factor induced.INR	RelTime	Pt	PPP	Qn	Coag	26
D-dimer	3246-6	Fibrin D-dimer	ACnc	Pt	PPP	Qn	IA	1
	38898-3[a]	Fibrin D-dimer	Titr[a]	Pt	PPP	Qn		1
	48058-2	Fibrin D-dimer DDU	MCnc	Pt	PPP	Qn	IA	3
	48065-7	Fibrin D-dimer FEU	MCnc	Pt	PPP	Qn		20
	48066-5	Fibrin D-dimer DDU	MCnc	Pt	PPP	Qn		2
	48067-3	Fibrin D-dimer FEU	MCnc	Pt	PPP	Qn	IA	1
	71427-9[a]	Fibrin D-dimer FEU	MCnc	Pt	Bld[a]	Qn	IA	1
	7799-0	Fibrin D-dimer	ACnc	Pt	PPP	Qn		4
Fibrinogen	30226-5[a]	Fibrin+fibrinogen fragments[a]	MCnc	Pt	PPP	Qn		2
	3255-7	Fibrinogen	MCnc	Pt	PPP	Qn	Coag	32
	48664-7	Fibrinogen	MCnc	Pt	PPP	Qn	Coag.derived	1
FDP, plasma	27810-1[a]	Plasmin inhibitor actual/normal[a]	RelCnc[a]	Pt	PPP	Qn	Chromo[a]	1
	30226-5	Fibrin+fibrinogen fragments	MCnc	Pt	PPP	Qn		4
	3251-6[a]	Fibrin+fibrinogen fragments	ACnc[a]	Pt	PPP	Qn	LA	1
	3252-4[a]	Fibrin+fibrinogen fragments	ACnc[a]	Pt	Ser[a]	Qn	LA	1
FDP, serum	**29991-7**	Fibrin+fibrinogen fragments	MCnc	Pt	Ser	Qn	LA	1
	30009-5	Fibrin+fibrinogen fragments	MCnc	Pt	Ser	Qn		1
	3251-6[a]	Fibrin+fibrinogen fragments	ACnc[a]	Pt	PPP[a]	Qn	LA	3

Abbreviations: ACnc, arbitrary concentration; APTT, activated partial thromboplastin time; Bld, whole blood; Chromo, chromogenic method; Coag, coagulation; DDU, d-dimer units; FDP, fibrin(ogen) degradation products; FEU, fibrinogen-equivalent-units; IA, enzymatic immunoassay; INR, international normalized ratio; LA, latex agglutination; LOINC, Logical Observation Identifiers Names and Codes; MCnc, mass concentration; PPP, platelet-poor plasma; PT, prothrombin time; Pt, single point in time; Qn, quantitative; RelCnc, relative concentration; RelTime, relative time; Ser, serum; Titr, titer.

The 6 LOINC code dimensions (axes/parts) of the fully specified LOINC code name, which describe the attributes of the observation, are the component (or analyte) being measured, the property being measured, the timing of the measurement, the system (sample type), the scale of measurement, and the method used to produce the observation. Of note, only the method axis is optional. Some of the parts are divided up into subparts, which can serve as modifiers and are separated by carats (^); the subparts can contain multiple levels of increasing taxonomic specification, separated by dots (.). For the system axis, when the specimen does not originate from the patient, the modifier (subpart) identifies the origin of the specimen.

Each axis of the LOINC code was assessed independently for appropriateness, and codes with errors in any of the LOINC axes/parts or in the order/observation field were identified.

Bold print indicates correct LOINC codes.

[a] Indicates incorrect LOINC codes and incorrect LOINC code axes.

For an Activated Partial Thromboplastin Time (aPTT) test, labs reported five different LOINC® codes that could be selected. Results differed due to different selections for the following axes:

- Component – One lab reported using the code 3184-9 for an aPTT test, which used a component "activated clotting time" instead of "coagulation surface induced"

- System – Between the different labs, some codes selected had the system as control blood (Bld^Control), platelet-poor plasma (PPP), or whole blood (Bld).

For a Prothrombin Time (PT) test, labs reported three different LOINC® codes that could be selected. Results differed due to some labs incorrectly selecting panels or the wrong system. For a D-Dimer test, results differed to differences in component, property, system, and method.

As referenced in the table "Correspondence of SNOMED CT® to Ciminos Desiderata", many of the errors occurred from different selections in system, where the system could be whole blood or platelet form plasma. "For the analyzers used by the laboratories in this survey, coagulation tests such as APTT and International Normalized Ratio (INR) are performed on PPP and are never performed on whole blood, so the selection of a code that indicates the system as PPP would more accurately represent the test performed as opposed to a code that lists the system as blood (Bld). Superficially, an end-user may think that "Bld" is a nonspecific answer for a collected blood specimen. However, LOINC® has defined the system part term Bld as whole blood as indicated in section 2.5 of the LOINC® User's Guide V2.65."

LOINC® is an international standard which means that there are terms that only apply to foreign assays but are still available for use by laboratories in the U.S. This results in concepts such as “Whole Blood” that mean something different than intended. End-users commonly use this concept when they intend to represent “platelet form plasma”; this results in highly prevalent errors in CoAg testing because the LOINC® concept for “Whole Blood” is perceived to be a general term when it is not. [15]

1.7.2.2. Issues with Granularity and Specificity

A study assessing LOINC® consistency at three different institutions found “inconsistency across institutions regarding specificity of mappings as they relate to methods. It appears that sometimes mappers link the method specific codes to a more general LOINC® code, and at other times they link to a method specific LOINC® code. This causes inconsistency in mappings across institutions.” [17]

Case Study 2: Comparison of LOINC® Codes between IVD Manufacturers and Medical Center Laboratories [20]

In an assessment of LOINC® interoperability between diagnostic test manufacturers and five medical center laboratories, there were mismatches related to granularity identified such as discrepancies between choosing:

- A methodless LOINC® code (e.g., 1920-8, Aspartate aminotransferase(AST),) instead of specific code including the method (e.g., 30239-8, Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma by With P-5’-P)
- A Quantitative LOINC® code (e.g., 70143-4, Cannobinoid screen) versus qualitative LOINC® code (e.g., 8172-9, Cannabinoids) by the manufacturer
- Different units of measure: mass/volume (e.g., 3094-0, Urea nitrogen [Mass/volume] in Serum or Plasma) versus moles/volume (e.g., 1493-7, Urea nitrogen [Moles/volume] in Serum or Plasma) [18]

1.7.2.3. Variation in Results for Different Devices

In addition to variation between how labs classify certain tests, there can also be variation in test results from manufacturers.

Case Study 3: D-Dimer Test Results from Different In-Vitro Diagnostic (IVD) Devices [15]

Figure 1.2, “D-Dimer Test Results from Different Devices” represents data results for D-Dimer tests that are all represented by the same LOINC® code. However, upon closer notice, the means between the different devices are significantly different. This raises concern amongst comparing data across institutions that use different devices.

Figure 1.2. D-Dimer Test Results from Different Devices

LOINC CODE
48067-3

LONG COMMON NAME
Fibrin D-dimer FEU [Mass/volume] in Platelet poor plasma by Immunoassay

LOINC STATUS
Active

D-dimer Quantitative

	CG-DD1							CG-DD2						
UOM/REAGENT/RESULT	LABS	MEAN	SD	CV	MEDIAN	LOW	HIGH	LABS	MEAN	SD	CV	MEDIAN	LOW	HIGH
mg/L or µg/mL FEU														
DIAG STAGO LIATEST	1269	1.494	0.079	5.3	1.49	1.05	2.04	1193	0.350	0.052	14.9	0.35	0.20	0.59
HEMOSIL D-DIMER HS 500	101	1.944	0.099	5.1	1.94	1.69	2.22	101	0.418	0.040	9.5	0.41	0.32	0.54
LSI MEDINC PATHFAST	-	-	-	-	-	-	-	10	0.713	0.056	7.9	0.73	0.62	0.80
ROCHE COBAS c SERIES	28	0.771	0.102	13.2	0.76	0.60	0.97	28	0.290	0.054	18.5	0.28	0.20	0.41
SIEMENS INNOVANCE	780	2.109	0.135	6.4	2.10	1.64	2.62	771	0.363	0.039	10.6	0.36	0.28	0.49
ng/mL or µg/L FEU														
BIOMERIEUX VIDAS/3/MINI	76	1790.688	107.714	6.0	1793.45	1591.20	2082.00	76	350.363	23.534	6.7	348.50	301.84	413.00
DIAG STAGO LIATEST	84	1486.417	66.350	4.5	1487.87	1320.00	1640.00	76	347.723	58.571	16.8	330.00	200.00	530.00
HEMOSIL (ACL 7/8/9/10K,ELITE)	16	1139.843	169.104	14.8	1095.50	1002.00	1715.00	20	439.567	61.216	13.9	453.37	287.00	527.00
HEMOSIL D-DIMER HS 500	533	1955.603	113.904	5.8	1952.70	1603.00	2337.00	532	427.521	48.968	11.5	428.00	260.00	594.00
SIEMENS INNOVANCE	81	2091.358	106.005	5.1	2091.50	1845.00	2400.00	80	358.788	33.580	9.4	350.00	290.00	460.00
SIEMENS STRATUS CS	17	1524.235	70.950	4.7	1524.00	1408.00	1709.00	18	363.444	18.834	5.2	360.00	335.00	399.00

The aforementioned CAP study surveying laboratories found that for a D-Dimer test, results differed to differences in component, property, system, and method. [12] Therefore, there is not only variation in test results from different devices and D-Dimer results, but there is also additional variation in the ability to encode the same test from a single device.

1.7.2.4. Manual Mapping Between Institutions

Due to the described inconsistencies between institutions, there is additional manpower required to determine comparable LOINC® codes. At many institutions, there are designated teams of doctors who must manually review submitted data to their institution to ensure that codes can accurately be compared between existing data in their system. [15] This process results in a cumbersome workflow process that involves personnel who must compare LOINC® codes, assess the validity of codes, and submit reviewal processes for codes that must be corrected.

Case Study 4: Bone-Marrow Transplant Research Study [15]

An academic medical center in Texas is conducting a bone-marrow transplant research center study, in order to build an interface that will allow users to automatically submit data to the hospital. However, upon review, there are issues where the LOINC® codes do not match correctly.

Figure 1.3. LOINC® Codes Used at Two Different Institutions for the Same Tests

Component	Our LOINC	Their Expected LOINC
Absolute Neutrophil Count (manual)	763-3	753-4
Metamyelocytes %	74428-4	740-1
Myelocytes %	74425-0	749-2
Reticulocytes % (automated)	42810-2	17849-1
Reticulocytes % (manual)	31111-8	(unknown based on spreadsheet)

Figure 1.3, "LOINC® Codes Used at Two Different Institutions for the Same Tests" provides insight into the difficulties doctors and technicians face in ensuring data mapped between systems are the same. Without high confidence in data, these issues can lead to impacts on real-world evidence capabilities.

1.7.2.5. LOINC® Should Define Relations (Using Description Logic)

LOINC® should define the relations between codes and combinations of codes that allow users to infer equivalence if their meanings in data instance representation are interoperable. That is, if the combination

of two codes has the same meaning as a single code (a difference in the use of pre- or post-coordination), relationships should exist between the codes that support the assertion of equivalence. Use of a Description Logics reasoner can help in overcoming important drawbacks of multi-axial systems: (1) the capability of detecting semantic equivalence of syntactically different expressions, and (2) the automated classification of concepts in a hierarchy.

1.7.3. Current LOINC® Efforts to Improve Interoperability

1.7.3.1. LOINC®-to-IVD (LIVD) Manufacturer Specifications

The LOINC® to IVD (LIVD) Mapping Specification is required by the United States Department of Health and Human Services for SARS-CoV-2 reporting and harmonizes how IVD test information is represented using LOINC®. The LIVD file format is currently led by IVD Industry Connectivity Consortium (IICC), and the JavaScript Object Notation (JSON) representation is a project at HL7.

To quantify the magnitude of problems that the lab data ecosystem faces, Cholan et al. describes a pilot evaluation with five healthcare systems that found LOINC® data maintained only 59% integrity as it moved from laboratory analyzer to laboratory information system. [20] Efforts to promote interoperability using LOINC® and related standards will require a more comprehensive effort and continuing evaluation and quality control.

1.7.4. Current LOINC® Improvements and Extensions of the Existing Hierarchy

1.7.4.1. Quality Assurance in LOINC® Using Description Logic

Although LOINC® has not officially adopted Description Logic and formal knowledge representation languages, the U.S. National Library of Medicine applied Description Logic to the quality assurance of LOINC® (based on the 2013 collaborative agreement) and used it as a basis for auditing LOINC®. [19] This study helps demonstrate the usefulness of Description Logic for terminologies by producing the following findings:

- 427 sets of logically equivalent LOINC® codes
- 676 sets of logically equivalent LOINC® parts
- 239 consistencies in LOINC® multi axial hierarchy
- Automated classification of LOINC® and SNOMED CT® increased connectivity by an additional 9000 LOINC® codes

Overall, these results suggest decent quality maintenance for LOINC® as these counts are relatively small considering the 450k+ concepts in LOINC® as part of this study. However, the key takeaway from this body of work is that LOINC® could benefit from the application of Description Logic by allowing for automated classification and equivalence detection. [19]

1.7.4.2. LOINC® Document Ontology

The LOINC® Document Ontology is a special set of LOINC® codes that are built on a framework for naming and classifying the key attributes of clinical documents. The codes intend to provide consistent semantics for documents exchanged between systems for many uses. The LOINC® Document Ontology represents the five key attributes of clinical documents that intend to be understood across systems.

- **Subject Matter Domain** e.g., Cardiology, Pediatric Cardiology, Physical Therapy

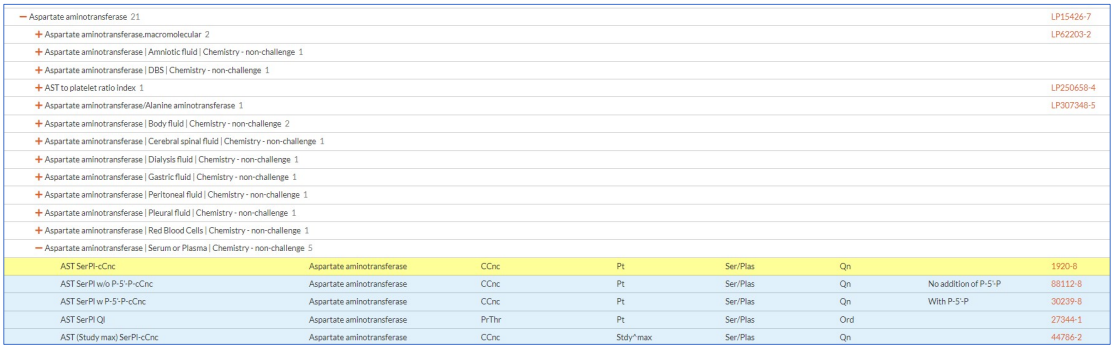
- **Role** *e.g., Physician, Nurse, Case Manager, Therapist, Patient*
- **Setting** *e.g., Hospital, Outpatient, Emergency Department*
- **Type of Service** *e.g., Consultation, History and Physical, Discharge Summary*
- **Kind of Document** *e.g., Note, Letter, Consent*

A semi structured interview conducted by consultants to government agencies and pathology experts produced a finding that the “LOINC® document ontology appears to be irrelevant to move things – not many people use it. It was a first attempt to apply some relationships between LOINC®'s concepts that formally don’t exist now, but it’s in a domain with low impact. [20]

1.7.4.3. LOINC® Hierarchy Browser

LOINC’s® website currently hosts ‘The Hierarchy Browser’ tool which allows users to view various hierarchies located in LOINC®. Much of this functionality was previously only available in the RELMA® application. [22] While a good starting point towards formal knowledge representation, the current hierarchies are limited, and still do not provide full definitions for LOINC® parts. Furthermore, the use of the hierarchies and LOINC® parts are very restricted under the LOINC® Copyright Notice and License. [22]

Figure 1.4. Representation of AST in The LOINC® Hierarchy Browser Tool



1.7.4.4. Nebraska Lexicon

The following excerpt provides background on the Nebraska Lexicon, a project focused on the harmonization between LOINC® and SNOMED CT®:

Since February 2004, University of Nebraska Medical Center (Nebraska Medicine) has maintained an extension namespace (extension identifier 1000004 registered with International Health Terminology Standards Development Organization (IHTSDO)) to support clinical terminology development required for electronic health record (EHR) deployment at its hospital and clinics. Content developed for this namespace has been driven pragmatically by recording requirements reported by Nebraska clinicians in the course of their daily work. This content has been deployed in records over three generations of EHRs including the Public Health Automated Medical Information System (PHAMIS), IDX-GE and now is in use in Epic®…

…In 2014, the Observables project of the IHTSDO and Regenstrief Institute published a draft convergent concept model for harmonization of content between LOINC® and SNOMED CT®. In January 2017, the project published a set of SNOMED CT® formatted expressions that define the meaning of ~13000 laboratory LOINC® observables employing the harmonized concept model. An expanded technology preview of ~20,000 concepts has been released by the IHTSDO but is not included in this publication. UNMC has converted the earlier expression set into SNOMED CT® formatted extension concepts employing LOINC® long names as the SNOMED CT® fully specified name and assigning class supertypes within

the Observable entity hierarchy in SNOMED CT®. 'Grouper' concepts have been modeled and deployed within the Observable entity hierarchy in order to enhance clinical navigation and to support common query use cases in laboratory medicine and pathology. Anatomic and molecular pathology observables defined by semantic analysis of the CAP Annotated Cancer Protocols explained in 3.3 are included. Some pre-existing SNOMED CT® Observable entity content has been fully defined using the harmonized concept model with permission of the IHTSDO. Grouper concepts have been included to organize the ontology and support common query use cases proposed by CAP. All content was run through the description logic classifier and both 'stated' and 'inferred' relationships are included in this release. This "Observables ontology" for laboratory medicine and pathology is being published for evaluation and comment by the informatics community. [23]

The Nebraska Lexicon is a pragmatic example of harmonizing terminologies into a single concept model and melding LOINC® and SNOMED CT® together. The content is published with permission of the CAP. A common terminology data model that expands beyond just LOINC® and SNOMED®, but that could also represent additional terminologies such as RxNorm, CVX, etc. (i.e., HL7's Terminology Knowledge Architecture) would allow users to integrate content and changes more seamlessly and reduce duplicative work

1.7.4.5. Quality Control

Current quality control of LOINC® is limited or not known. While the aforementioned Quality Assurance study proved that use of Description Logic is promising and beneficial for terminologies such as LOINC®, these types of quality assurance methods are not widely used.

The only published quality metrics from Regenstrief about LOINC® include published stats about their submission queue describing how long it takes to create a LOINC® term (e.g., 182 days to turn around a revision). [24]

Regenstrief relies on an occasional survey (either once per year or once every few years) from ONC to the laboratory community to assess how labs are using LOINC®, what are the barriers, etc.; however, the survey is very LOINC®-centric and not so much about the quality of the terminology standard itself.

LOINC® is user-driven, so all submissions are coming from the community. This is beneficial in that there is transparency and openness to the curation of content. However, the current curation is inadequate, and there is no systemic approach to ensure no overlap between terms.

1.7.4.6. Educational Workshops

There are paid workshops users can attend in association with LOINC® meetings. These workshops tell users how to go about using LOINC® codes and how to use RELMA®. In a semi-structured interview with participants from the public and private sectors, it was stated that "the helpfulness and usefulness of these educational workshops may be in question by some stakeholders in the community."

1.7.5. Future Policy and Direction for LOINC®

1.7.5.1. Improved Education

Improving education through established certification programs, improved structure in the community, and more training are potential next steps.

1.7.5.2. Robust Quality Control

LOINC® may need more pruning of extraneous terms and duplicate terms. There is also potential room for refining the different levels of granularity of terms.

1.7.6. RxNorm Existing Limitations

1.7.6.1. Lack of Description Logics

RxNorm lack of Description Logics formalism use, as proposed by SOLOR, limits its ability to use logic reasoners for inferencing. This limits RxNorms ability to find new patterns, relationships and identification of equivalence. [1]

1.7.6.2. Concerns Over Concept Permanence

While RxNorm CUIs are never reused as per best practice, the possibility exists that RxNorm atoms can change with the potential to change the definition. Furthermore, RxNorm CUIs that are no longer in RXNCONSO are moved to a cumulative archive called RXNATOMARCHIVE.

1.7.6.3. Formal Concept Definition

While RxNorm has ‘defined ingredients’, historically it has lacked the computational ability to define concepts by relationships, thereby allowing inferencing. [26] However, recent efforts by Bona et al. have successfully created an OWL file to implement and define the classes necessary to model RxNorm and NDC concepts. [13]

1.7.7. Future Harmonization of Standards

In the U.S., SNOMED CT® and RxNorm are harmonized but LOINC® has not joined the harmonization. There have been some partnerships and independently funded programs to help make LOINC® more compatible and useful within the ecosystem of controlled medical terminologies that converge on a model of meaning that can be shared. Further integration has been proposed but will require additional resources to bring these terminologies closer together. However, the collaboration between SNOMED CT® and LOINC® has been renewed. Create a LOINC® extension of SNOMED CT® to leverage the strengths of both has been the popular notion. This notion has been particularly attractive for the SNOMED CT®'s polyhierarchal structure and inferencing capabilities. This concept leads to embrace a greater compatibility and interoperability, integration of SNOMED CT®, LOINC®, and RxNorm, while noting different formalisms and tools for their representation in these technologies. [26] Various terminologies have different semantics, models, release cycles, and versioning mechanisms. [1] While there is recognition that terminologies are not standardized at the exchange level, there is no consensus about harmonized next steps to solve the challenges.

Today, we recognize many popular movements in both private and public sectors to set strategies to transform many aspects of laboratory ecosystem into an interoperable system. We strive to achieve the goal of unifying industry coding standards, such as LOINC®, to create a reference knowledge base where any user of laboratory data can obtain more information about the performed test in question.

1.8. Terminology Knowledge Example

In this section, we will be discussing a use case using questionnaires and responses.

1.8.1. Terminology Knowledge Problem Statement

As a real-world use case, we focused on improving the diagnosis of emerging acute chronic infectious diseases, initially focusing on Long COVID as an example. There are numerous areas within clinical workflows for COVID-19 exposure and Long COVID diagnosis that are open to improvements that will

ultimately help provide safe and effective patient care. There is a need to determine clear prioritization principles around focus areas for data capture within these COVID-19 workflows. To date, Long COVID has been primarily a diagnosis of exclusion, meaning that it is often only diagnosed after all other conditions are eliminated as a possible cause of symptoms. Clinicians need to make quick decisions based on objective and subjective observations to determine if a patient has signs and symptoms compatible with Long COVID and whether the patient should be admitted to the hospital. Clinicians are encouraged to leverage technology, virtual visits, and other Health Information Technology (IT)-generated clinical data to assist with decision making and information sharing. Unfortunately, electronic clinical data is plagued by data quality challenges, including variation in how data elements are encoded by terminology standards, and stored in clinical information models. These challenges can cause inefficiencies in how clinical data elements are identified, retrieved, analyzed, and operationalized into workflows at the point-of-care.

In the current workflows for COVID-19 and Long COVID, clinicians are encouraged to rely on electronic clinical data to determine which patients should be prioritized for being tested, hospitalized, and/or isolated. Failure to include or exclude patients' screening, testing, and treatment could lead to life-threatening situations for patients and could impact the overall trajectory of the outbreak at a population-level. Overall, the ability to measure and improve healthcare outcomes relies on consistent, high-quality electronic data that is aggregated from a variety of Health IT systems across numerous medical centers and healthcare facilities. Clinicians need to be able to easily access and fully trust the electronic data they are using to make determinations at the point-of-care, key components of High Reliability Organizations and Learning Health Systems.

Using ANF as a standardized statement model to streamline analysis could potentially lead to improved and earlier Long COVID diagnoses. This body of work aims to focus on workflow areas of data as it is captured for Long COVID – perhaps iPad data entry, EHR collection of signs and symptoms, emergency warning signs, patient-reported data, etc. – to understand how the collection of data elements in a consistent and high-quality manner, and the subsequent data analysis, fit into the overall goal of achieving coordinated, national and highly-reliable care.

1.8.2. Terminology Knowledge Demonstration Objectives

The objective of this work is to document data collection methods and statement model standards to demonstrate the importance of an interoperable data system and downstream analytical scenarios through a use case for Long COVID as an example of an emerging acute chronic infectious disease. We aim to highlight how Analysis Normal Form (ANF) can be used to standardize the representation of equivalent concepts associated with data capture, storage and aggregation within the Long COVID workflow. This work utilized four main aims to demonstrate how ANF-thinking could improve use case outcomes and reduce the clinical burden on data consumers during data collection and aggregation:

Aim 1: Review Workflow Schematic for Emerging Acute Chronic Infectious Diseases, specifically focused on Data Capture Elements and Long COVID Value Sets

Aim 2: Draft Potential Questionnaires to Standardize Use Case Data Acquisition

Aim 3: Outline Variability in Statement Representations

Aim 4: Demonstrate ANF Ability to Standardize Terminology and Capture Critical Data

1.8.3. Terminology Knowledge Methods

Aim 1: Review Workflow Schematic for Emerging Acute Chronic Infectious Diseases, specifically focused on Data Capture Elements and Long COVID Value Sets. In support of Task 3.2.1, our team documented a generalized workflow and use case schematic for a patient's journey from COVID-19 exposure to Long COVID diagnosis. We focused on decision points related to data capture of signs and symptoms related

to COVID-19 and outlined key terminology and clinical information modeling considerations within the workflow artifacts that were developed.

The team then gathered and reviewed value sets from the National Institute of Health's (NIH) National Library of Medicine (NLM) Value Set Authority Center (VSAC) to identify common concepts and data elements that would need to be captured to support a Long COVID diagnosis. Each team member was assigned a value set and identified common and well documented concepts from their respective set, including signs and symptoms, laboratory tests, laboratory test results, potential and confirmed exposure, and suspected and confirmed infection. The concepts were organized by value set and documented in a table.

Aim 2: Draft Potential Questionnaires to Standardize Use Case Data Acquisition. Long COVID is a poorly understood condition where patients experience COVID-19 symptoms long past the expected symptomatic period and whose symptoms, test results, and timelines can vary drastically between patients. The team developed sample questionnaires based on the VSAC value sets to collect additional data that patients or providers could enter into a Clinical Input Form or questionnaire. Traditional, current-state questionnaires were developed for the Long COVID use case to demonstrate how users may struggle to identify the optimal selections to document certain symptoms and may result in inconsistent and/or duplicative clinical data. The team then worked to develop an improved questionnaire that removes redundant and vague concepts and forces more granular and detailed selections to highlight ways to enhance the quality, accuracy, and interoperability of collected data.

Aim 3: Outline Variability in Statement Representations. Current terminology standards vary in the way they represent and code many data points that can be acquired through patient questionnaires. Critical information regarding severity, site, associated concepts, and data elements can be spread across the respective fields, incorporated directly into the concept code, or a combination of the two. The table aims to highlight the need for a normalized way to represent concepts to prevent loss of critical data and meaning as it is transformed and transmitted within and between systems. Improving the data collection, encoding, and storage of both present and absent concepts is essential in the effort to achieve lossless and interoperable data.

Aim 4: Demonstrate ANF Ability to Standardize Terminology and Capture Critical Data. This paper ultimately aims to improve the acquisition, storage, and use of data across a variety of clinical situations, with the Long COVID use case as an example. We propose ANF as the tool to standardize and normalize the way critical data concepts from patient questionnaires are represented before transmitting to other systems for secondary use. The same concepts that were shown to have varying representations across terminology standards were modeled using a tabular ANF representation to demonstrate how ANF captures the same or more detail as other standards and normalizes the formatting of equivalent concepts across terminologies. The ANF table captures key data elements for the concept of loss of sense of smell since onset of COVID-19 symptoms. The concept ID, author, and topic are clearly documented along with timing of onset and recording. Not only is the concept itself represented in a normalized way that captures all pertinent values and details, but other normalized concepts, like linking to the beginning of symptom onset can be linked as associated clinical statements that add additional value and context.

1.8.4. Terminology Knowledge Example Results

Aim 1: Review Workflow Schematic for Emerging Acute Chronic Infectious Diseases, specifically focused on Data Capture Elements and Long COVID Value Sets. The team downloaded and reviewed the COVID-19 VSAC value sets outlined in the table below. The team used these value sets to extract an initial list of generalized clinical concepts associated with a COVID-19 diagnosis that could potentially contribute to a Long COVID diagnosis. [27]

Table 1.5. VSAC Value Sets

Value Set Name	Steward	Value Set OID

COVID19 Potential Signs and Symptoms	CareEvolution	2.16.840.1.113762.1.4.1223.22
Nonspecific Respiratory Viral Infection	CareEvolution	2.16.840.1.113762.1.4.1223.25
C19HCC SARSCoV2 Exposure	MITRE	2.16.840.1.113762.1.4.1032.120
COVID19 Potential Exposure	CareEvolution	2.16.840.1.113762.1.4.1223.18
COVID19 Suspected Infection	CareEvolution	2.16.840.1.113762.1.4.1223.6
LIVD SARS CoV2 Test Codes	ONC	2.16.840.1.113762.1.4.1114.9
LIVD SARS CoV2 Test Result Codes	ONC	2.16.840.1.113762.1.4.1114.10

Aim 2: Draft Potential Questionnaires to Standardize Use Case Data Acquisition. An initial questionnaire was developed for the generalized concepts extracted from the COVID-19 VSAC value sets that poses a simple yes or no question for each of the concepts that could potentially aid in a Long COVID diagnosis. This chapter focuses on potential questionnaires for 'Signs and Symptoms' and 'Non-Specific Respiratory Diagnoses', outlined in Figure 1.5, "Hypothetical Signs and Symptoms Questionnaires" and Figure 1.6, "Hypothetical Non-Specific Respiratory Diagnoses Questionnaire" respectively. [2]

Figure 1.5. Hypothetical Signs and Symptoms Questionnaires

Signs And Symptoms	Yes	No
Abnormal Breath Sounds		
Abnormalities Of Breathing		
Aching Headache		
Chills (Without Fever)		
Complaining Of Vomiting		
Cough		
Difficulty Breathing		
Dry Cough		
Dyspnea		
Fever		
Fever Greater Than 100.4 Fahrenheit		
Fever With Chills		
Headache		
Intermittent Fever		
Other Abnormalities Of Breathing		
Parietal Headache		
Productive Cough		
Shortness Of Breath		
Short Of Breath		
Spiking Fever		
Tachypnea		

Improved Signs And Symptoms	Yes	No
Breathing Difficulties		
• Abnormal Breath Sounds		
• Difficulty Breathing		
• Shortness of Breath		
• Rapid Breathing		
• Other Abnormalities of Breathing		
Cough		
• Productive Cough (Producing Phlegm)		
• Dry Cough		
Fatigue		
Fever		
• Fever Less than 100.4 Fahrenheit		
• Fever Greater Than 100.4 Fahrenheit		
• Intermittent Fever		
• Spiking Fever		
Headache		
• Aching Headache		
• Parietal Headache		
Sensory Alteration		
• Loss of Taste		
• Loss of Smell		
• Sense of Smell Altered		
• Sense of Taste Altered		

While the initial version of the questionnaire on the left can collect important information and data, the format was improved in the version on the right to reduce redundancy, improve clarity, and collect more

accurate and granular detail. The improved questionnaire forces patients or physicians completing the survey to select more granular symptoms and reduces ambiguity. Rather than allowing for individuals to select 'cough' and 'dry cough' or 'productive cough', the improved questionnaire forces a more accurate selection of either 'dry cough' or 'productive cough' to reduce redundant data. Additionally, the improved questionnaire utilizes user-friendly definitions like rapid breathing rather than highly technical terminology like 'tachypnea' to reduce duplicative symptoms and support accurate data collection from a wider audience. The value sets and questionnaires will need to be updated as symptoms are more comprehensively understood, and as new symptoms are identified.

The team developed additional questionnaires for non-specific respiratory diagnoses below in Figure 1.6, "Hypothetical Non-Specific Respiratory Diagnoses Questionnaire". The diagnoses questionnaires continue to improve data quality by reducing duplicative selections and improving granularity by forcing an Upper or Lower 'Viral Respiratory Tract Infection' rather than allowing the selection of both Upper or Lower Viral Respiratory Tract Infection and "Viral Respiratory Tract Infection'. These additional questionnaires demonstrate how improvements can be made to data collection across a variety of areas associated with patient care and can be applied to other emerging acute and chronic infectious diseases.

Figure 1.6. Hypothetical Non-Specific Respiratory Diagnoses Questionnaire

Non-Specific Respiratory Diagnoses		
	Yes	No
Upper Respiratory Infection		
Lower Respiratory Infection		
Viral Upper Respiratory Tract Infection		
Viral Lower Respiratory Tract Infection		
Viral Respiratory Tract Infection		
Other Specified Respiratory Disorders		

Improved Non-Specific Respiratory Diagnoses		
	Yes	No
Respiratory Infection		
• Upper Respiratory Infection		
• Lower Respiratory Infection		
• Viral Upper Respiratory Tract Infection		
• Viral Lower Respiratory Tract Infection		
Other Specified Respiratory Disorders		

Aim 3: Outline Variability in Statement Representations. Building upon the concepts found in the VSAC value sets, the team developed tabular representations of certain symptoms to display the variability in the way concepts could be represented and coded. Figure 1.6, "Hypothetical Non-Specific Respiratory Diagnoses Questionnaire" depicts the symptom of 'Fever Greater Than 100.4 Fahrenheit with Chills' across three example terminology standards as well as the null value of a normal body temperature. After reviewing the table, one could conclude that the first three examples are semantically the same. Each describe a condition of fever greater than 100.4 Fahrenheit, but critical information is spread out across the severity, site, and code fields depending on how the respective terminology standard represents the condition. This variability leads to sub-optimal data capture that can hinder data querying, data use, and the ability to identify semantically equivalent concepts.

Table 1.6. Variability in Representation of Fever

	COVID19 Symptoms Present Example 1	**COVID19 Symptoms Present Example 2**	**COVID19 Symptoms Present Example 3**	**COVID19 Symptoms Absent**
Condition	Fever Greater Than 100.4 Fahrenheit with Chills Present	Fever Greater Than 100.4 Fahrenheit with Chills Present	Fever Greater Than 100.4 Fahrenheit with Chills Present	Body Temperature Within Normal Range

…..	**…..**	**…..**	**…..**	**…..**
Severity	Null	Greater than 100.4 Fahrenheit	Greater than 100.4 Fahrenheit	Between 97.6 and 99.6 Fahrenheit
Code	Fever Greater Than 100.4 Fahrenheit with Chills (finding)	Fever with Chills (finding)	Fever with Chills (finding)	Regular Body Temperature (finding)
Site	Null	Null	Mouth/Tongue	Null

Aim 4: Demonstrate ANF Ability to Standardize Terminology and Capture Critical Data. The team demonstrated the value of ANF by developing a tabular ANF representation for loss of sense of smell since onset of COVID-19 symptoms. ANF provides a singular, normalized way to represent concepts from different terminology standards by restricting various data elements to certain fields, like the severity of a particular symptom in the results section. Standardizing how data elements are reported facilitates the identification of equivalent terminology and improves the quality and interoperability of data. In the example below, ANF captures all the pertinent information including the symptom itself, option for the severity or numerical value of an observation, and the method of the observation, as well as additional information like the timeframe when a symptom first occurred. This additional information is an associated term that adds value and context to a measurement.

While documenting symptoms that are marked as present on the improved questionnaire in a normalized format is essential, it is also important to represent signs and symptoms that are absent in a patient. Corresponding present and absent concepts for a certain symptom do not always exist across terminology standards, but ANF is able to represent the absence of a symptom using a numerical countable quantity, ensuring relevant and pertinent information is not lost.

Table 1.7. ANF Standardized Representation of Anosmia and Associated Term Narrative 1

Narrative 1: **Loss of Sense of Smell**	
id: **XXXXXXXX-XXXX-XXXX-XXXX-XXXXXXXXXXXX** time: **1:17pm 2023-02-14 T09:20:00.00+01:00** subjectOfRecordId: **Participant** author: **Healthcare Professional** subjectOfInformation: **Subject of Record** type: **Performance** topic: **Loss of Sense of Smell**	
Circumstance	PerformanceCircumstance
	• status: **[Complete]**

	• result: **[1,1]**
	  • resolution: **[N/A]**
	  • semantic: **[N/A]**

	• healthRisk: **[N/A]**

	• participant: **[Participant]**
	• referenceRange **[N/A]**
	• timing: **12:40pm 2023-02-14 T09:20:00.00+01:00**
	• purpose: **[N/A]**
Associations:	
associatedStatement: [UUID] (Table: Associated Clinical Statement 1)	

Table 1.8. ANF Standardized Representation of Anosmia and Associated Term Narrative 2

Narrative 2: **Since Onset of COVID-19 Symptoms**	
id: **[UUID] Associated Clinical Statement 1** time: **1:17pm 20123-02-14 T09:20:00.00+01:00** subjectOfRecordId: **Participant** author: **Healthcare professional** subjectOfInformation: **Subject of record** type: ***Observation Procedure*** topic: **Since onset of COVID symptoms**	
Circumstance	PerformanceCircumstance
	• status: **[Complete]**
	• result: **[1,1]** • resolution: **[N/A]** • semantic: **[N/A]**
	• healthRisk: **[N/A]**
	• participant: **[Participant]**
	• referenceRange: **[N/A]**
	• timing: **1:17pm 20123-02-14 T09:20:00.00+01:00**
	• purpose: **[N/A]**
Associations:	
associatedStatement: **[N/A]**	

1.8.5. Recommendations to Address Terminology Issues

This section aims to highlight some of the current shortcomings with the way data is collected and represented. We propose the following recommendations for data collection via patient questionnaires to reduce duplicative and vague data collection, facilitate secondary data usage, and improve data interoperability:

1. Restrict data entry and collection with pre-populated patient questionnaires based on established concepts from the appropriate value sets to standardize data collection. This will work when questionnaire designers and data consumers know the data that they are trying to capture. In the context of a condition where the signs and symptoms are less well defined, or have not yet been defined, this methodology may inhibit knowledge discovery and should be supported by integrated knowledge management constructs that facilitate data agility and regular updates to value sets.

2. Use detailed concepts to force granular selections that reduce ambiguity or the need for duplicative data in pre-populated patient questionnaires.

   Questionnaires should not allow the selection of just '*Cough*' and should prompt patients or providers to select if it is a '*Productive Cough*' or '*Dry Cough*'.

   Questionnaires should not allow the selection of '*Viral Respiratory Infection*' and should prompt patients or providers to select a body site or location like '*Upper Viral Respiratory Infection*' or '*Lower Viral Respiratory Infection*'.

3. Group concepts by critical information like '*Confirmed*' and '*Potential*' exposure to prevent accidental selection of inaccurate responses.

4. Add patient friendly terminology, like '*Rapid Breathing*', to value sets and questionnaires to facilitate the collection of critical patient health data from a wider audience rather than highly technical terms such as '*Tachypnea*'.

These recommendations can and should be applied across all data collection questionnaires, not just the 'Signs and Symptoms' and 'Non-Specific Respiratory Diagnosis' questionnaires represented in this chapter.

1.8.6. Technologies that Support ANF

While standardizing data collection methods is a critical step towards data interoperability and ANF data transformations, there are still common sources of errors associated with normalizing clinical data. Errors normalizing terminology content, terminology semantics, and poorly defined interactions between the input and presentation of clinical data are three key problems that still need to be addressed. Several transformation languages and architectures exist for expressing and executing transformation logic to address the issues above and to normalize specific instances of clinical data into ANF. Users can choose a language that is best tailored for the format of the data source, while transformation quality and accuracy is left to the transformation author. Below is a list of four transformation languages and the associated benefits and limitations. While each option has its own limitations and cost, the ability to address or minimize common normalization errors justifies their use. [27]

Table 1.9. Benefits and Limitations of Transformation Languages and Architecture

Standard or Language	Benefits	Limitations
eXtensible Stylesheet Language Transformation (XSLT)	• Robust language • Easily extensible via extension functions and calls • Auto matches templates to data • Easy tooling • Good documentation	• Transformation specifications are difficult to read and understand • Transformations are syntactic • XML input only, other formats not translated

Standard or Language	Benefits	Limitations
FHIR Mapping Language (FML)	• Supports input formats other XML • Semantic DAGs can be rendered in variety of syntaxes • Concise and easy to read mapping specifications	• Input and output outside of FHIR logical models require extra custom programming • Only XML and JSON supported as output syntaxes, otherwise custom programming is required • To date, only one implementation • Limited tools needed for editing and authoring scripts • Limited documentation sources • Limited pool of knowledgeable programmers
QVT	• Great flexibility and configurability to create custom transformation languages	• Limited learning resources making it difficult to learn and understand
Model Driven Message Interoperability (MDMI)	• Any-to-any transformations support reuse of transformation models for different use cases • Minimal changes to other models if model changes • Simplifies development, tooling supports development by SMEs and not dependent on developers • Enables automation tooling for models • Available open-source models for HL7 formats	• Limited experience working with transformations of detailed clinical models. • Lacking user documentation • Complex runtime tool

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Part II. Assertional Knowledge

Table of Contents

2. Assertional Knowledge

2.1. Introduction to Assertional Knowledge

Previously, we discussed terminology knowledge which does not represent how concepts influence or relate to each other in a clinical setting. This type of information is represented by assertional knowledge. For example, shortness of breath may be caused by myocardial infarction. Assertional knowledge represents facts related to a domain of study and is used to provide nuance and context to a concept, but does not define it. For example, Aspirin is used to treat pain, but it can also be used to treat fevers, prevent blood clots, reduce the risk of stroke and heart attack and many other things. The two major goals of including assertional knowledge are (1) to enhance usability and (2) improve documentation quality when using a terminology. Additional facts about clinical concepts can also be provided to support reasoning for automated quality monitoring and clinical decision support. [1]

Additionally, assertional knowledge supports interface implementation by providing increased synonymy that is specific as to the context in which it should be used. What has been previously called interface terminology can be defined as a "systematic collection of clinically oriented phrases (terms) whose purpose is to support clinicians' entry of patient information into computer programs, such as clinical note capture and decision support tools". [1]

This interface support is used to accomplish one of two tasks:

1. Encoding clinical narrative into a structured form, or
2. Reviewing structured clinical information that has previously been encoded using a different terminology.

This interface support must enable correct and rapid interaction between clinicians and structured clinical data, support ease of use by healthcare providers through easy understandability, and integrate well with other clinical computerized systems in the environment. [1]

Assertional knowledge is key to supporting interface implementation of the terminology layer. Assertional knowledge can support interface implementations of terminology by:

1. Assisting end users in adding clinical modifiers to concepts
2. Representing additional relationships for clinical concepts
3. Providing support for synonymy [1]

2.2. Adding Clinical Modifiers to Concepts

There are one of two general approaches to representing knowledge domains by clinical terminology.

In one approach, developers **precoordinate** (or enumerate) all possible complex concepts apriori and essentially create a list of all the complex concepts that can be expressed. A strength of this approach is increasing the chances a user will find a desired concept. Disadvantages include making a terminology so large that search becomes burdensome, and reduced flexibility in situations where the terminology does not contain concepts that a user may need.

An alternative is **postcoordination** in which users compose complex concepts by assembling general concepts and modifiers as needed. An advantage is increased flexibility for representing a wide range of concepts. Disadvantages include increased variation and inconsistent application of terminologies against

clinical data, increased ability to create nonsensical complex concepts from modifiers and concepts, and inefficiency since postcoordination processes can be time-consuming.

Bringing these two approaches together can optimize a terminology's flexibility, ease of use, and overall coverage. "Compositional balance" makes concept selection tasks efficient by reducing the effort to assemble complex concepts from general concepts, and reducing the time needed to search through long lists of precoordinated concepts.

Prior to 2012, SNOMED CT® included qualifying relationships that could be used for creating a user interface that would post-coordinate concepts using pre-approved attribute value pairs. With the introduction of the RF2, qualifying relationships were no longer released in favor of the Machine Readable Concept Model (MRCM). The MRCM is a more comprehensive and flexible format for representing relationships and values that can be used to refine concepts.

2.3. Representing Additional Relationships for Clinical Concepts

2.3.1. Facts Supporting Reasoning

Attributes like the ones below are common in proprietary interface terminologies and represent assertional knowledge that can then be mapped to standard reference terminologies like SNOMED CT® or RxNorm.

- “Aspirin treats pain”
- “Penicillin treats bacterial infections”
- “Myocardial infarction is associated with chest pain”

The United States Department of Veterans Affairs (VA's) National Drug File - Reference Terminology (NDF-RT) has assertional knowledge contained in relationships like:

- may_treat {} # DISEASE_KIND – therapeutic use or indication of a generic ingredient preparation or drug
- may_prevent {} # DISEASE_KIND – preventative use or indication of a generic ingredient preparation or drug
- may_diagnose {} # DISEASE_KIND – diagnostic use or indication of a generic ingredient preparation or drug

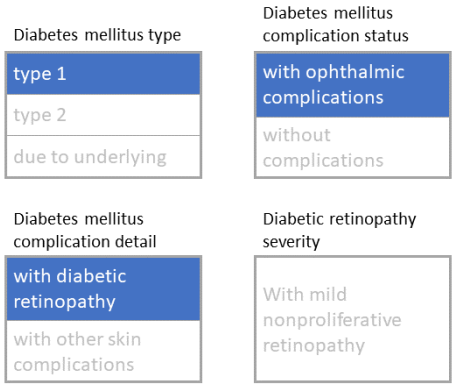
Structure Product Labeling has assertional knowledge contained in sections such as:

- Indications
- Contraindications

2.3.2. Representation of Concept Hierarchies

Ideally, a terminology is represented in a way to promote easy use for automated data storage, management, and analysis. Description logics can formally model and specify the relationships that exist among concepts and modifiers and provide a structured representation of the knowledge domain. For instance, in the following screenshot, when "Diabetes mellitus type 1" is selected, the options for "type 2" are hidden and de-emphasized to the user.

Figure 2.1. Interface Term



2.3.3. Relationships Between Clinical Concepts and Patient Populations

An example of a relationship between a clinical concept and patient population is pregnancy is not present in men or women who have had a hysterectomy or who are post-menopausal.

2.4. Support for Synonymy

2.4.1. Support for Human-Readability

The goal of interface terminologies is to optimize the user experience. Increasing efficiency and clarity of data review are key considerations for helping clinicians access, read, and understand encoded clinical data. A simple approach is to use relatively colloquial terms and display common phrases and words. More complex approaches include "auto-complete" features - when a user selects a concept (e.g., "chest pain") and modifiers (e.g., "anterior", "dull" "present"), the system may leverage tagged terminologies to generate the natural language sentence (e.g., "anterior dull chest pain is present").

2.4.2. Clarifying synonymy

Assertional knowledge relationships can be used to clarify whether synonyms are accurate representations of the same concept. For example, thorax pain and chest pain could be defined in a similar way, but thorax pain may imply to a healthcare provider that the pain is in the chest wall rather than internally as the term chest pain may imply.

2.4.3. Completeness of Synonym Coverage

An adequate representation of synonyms in a terminology can increase the terminology's usability. Terminologies should represent the richness present in colloquial phrases of medical discourse and represent the variety of different types of synonyms that exist:

Alternate Terms: "Myocardial Infarction" for "Heart Attack"

Acronyms: "MI" for "Myocardial Infarction"

Definitional phrases: "Ischemic injury" for "necrosis of heart muscle cells resulting from absent or diminished blood flow in a coronary artery"

Eponyms: "Levine sign" for "a clenched fist held over the chest indicating ischemic cardiac chest pain"

However, rich synonymys may increase the chances that a given term may be used to represent more than one concept (e.g., "cold" for "low temperature" and for "upper respiratory tract viral infection". Parameters for metrics for evaluating the completeness of synonym coverage in clinical interface terminologies include:

Concept Accuracy: how closely a term's meaning corresponds with the underlying concept it represents; and,

Synonym Expressivity: how well a term's semantic character matches the words in the phrase it is meant to represent rather than the underlying meaning.

For example a patient describes having a "feathery discomfort occurring across the chest". Within a clinical terminology, there is a concept for "chest discomfort" and modifiers like "soft" and "anterior chest wall". The end-user selects "noncrushing" to represent "feathery". The concept accuracy of "noncrushing" for "feathery" is adequate because the two have the same meaning. However, "noncrushing" does not fully express the character of "feathery".

2.5. Representation of Assertional Knowledge

Representation of Assertional Knowledge reaches beyond the patient as the subject of record and observations and evaluation results about the patient. It represents knowledge that can be applied to the patient's care, e.g. the patient's treatment or diagnostics.

The capability of associating statements enables the use of Assertional Knowledge to clinical decision support applications, clinical pathways and general information (“info button”) that can be made available to users of EMR systems.

2.6. References

1. Rosenbloom ST, Miller RA, Johnson KB, Elkin PL, Brown SH. Interface terminologies: Facilitating direct entry of clinical data into Electronic Health Record Systems. Journal of the American Medical Informatics Association. 2006;13(3):277–88. doi:10.1197/jamia.m1957

Part III. Procedural Knowledge

Table of Contents

3. Procedural Knowledge Representation

Generally, Procedural Knowledge can pertain to Clinical Decision Support (CDS), e.g.:

• Standard ways of performing a procedure

• Treatment protocols for diseases

• Standard evidence-based Order Sets

Applied Procedural Knowledge can enable the use of CDS, Clinical Pathways, and Knowledge Artifacts (KNARTs), that standardize patient documentation, quality improvement interventions, and protocols focused on specific clinical domains and patient situations.

3.1. Introduction to Clinical Decision Support (CDS)

As defined by Osheroff et al. CDS “provides clinicians, staff, patients, or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care.” [1] CDS encompasses a variety of tools to enhance decision-making in the clinical workflow. Examples of CDS tools include but are not limited to:

- order sets created for particular conditions or types of patients.
- recommendations/databases that can provide information relevant to particular patients.
- reminders for preventive care.
- documentation templates.
- diagnostic support.
- alerts about potentially dangerous situations.

Osheroff also published “The CDS 5 Rights framework” (5Rights) which asserts that, to improve targeted healthcare decisions/outcomes with well developed and deployed CDS interventions, the interventions must provide:

- the **right** information,
- to the **right** people,
- in the **right** intervention formats,
- through the **right** channels,
- at the **right** points in workflow. [1]

Understanding and leveraging effectively the 'what, who, how, where, when' information process/workflow dimensions is central to configuring useful CDS and Quality Improvement approaches.

A 2012 Literature Review commissioned by the Agency for Healthcare Research and Quality (AHRQ) found evidence showing that CDS had positive impact on process measures and increasing user knowledge relevant to a medical condition. [2]

Additional studies show that well-executed CDS can [2]:

- reduce adverse drug-drug interaction events and medication errors [3], [4], [5]
- decrease unnecessary lab testing [6]
- reduce cardiovascular risk in patients with type 2 diabetes [7]
- improve practitioner performance [8]
- increase cardiovascular disease risk assessment in routine primary care practice [9]
- improve public health outcomes associated with outbreaks of foodborne illness or/and [10]
- and, produce cost savings associated with hospital-based pharmacy interventions. [11]

The available evidence shows that CDS —when implemented properly with formal management—can reduce errors, improve the quality of care, reduce cost, and ease the cognitive burden on health care providers. [2] As a result, the impetus for achieving standardized, widespread adoption of CDS across health systems is clear. The American Medical Informatics Association (AMIA) CDS Roadmap Development Steering Committee describes three pillars for realizing this promise of CDS: [1]

1. **Best Knowledge Available When Needed**

   CDS is well organized, accessible, and written, stored and transmitted in a format that makes it easy to build and deploy CDS interventions that deliver the knowledge into decision-making.

2. **High Adoption and Effective Use**

   CDS tools are widely implemented, extensively used, and produce significant clinical value while making financial and operational sense to their end-users and purchasers.

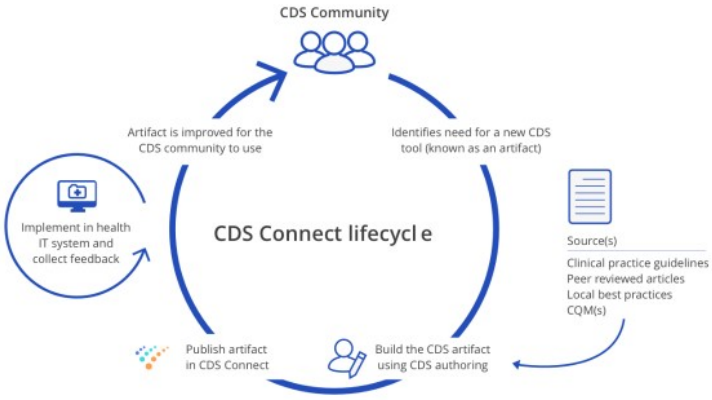
3. **Continuous Improvement of Knowledge and CDS Methods**

   Both CDS interventions and clinical knowledge undergo continuous improvement based on feedback, experience, and data that are easy to aggregate, assess, and apply. [1]

In order for the vision of the AMIA CDS Roadmap Steering Committee to be achieved, the science of CDS needs to support implementers, clinicians, and technology vendors in developing CDS tools that are shareable, standards-based, publicly-available, and patient-centered. Namely, the translation of evidence-based clinical practice guidelines into implementable clinical tools needs to occur in a manner that is consistent, systematic, and comprehensive. There have been a number of historical efforts that have aimed to achieve interoperable and robust CDS tools and artifacts that appropriately translate guidelines into care. The AHRQ depicts the following image representing the “CDS lifecycle” for the following areas: [1]

- Authoring CDS tools and artifacts that leverage knowledge sources such as clinical practice guidelines, quality measure specifications, and peer-reviewed journal articles
- Publishing CDS tools to a public repository (e.g., AHRQ’s CDS Connect)
- Implementing CDS tools in a community (i.e., learning network) and collecting on-the-ground stories and evaluation metrics to then inform the subsequent design, build, and implementation of future CDS tools

Figure 3.1. CDS Connect Lifestyle



3.2. Lack of Standardized Encoded Clinical Data - Impact on CDS

In this section, we will explore an important question regarding appropriate and highly-reliable CDS: ***how can we provide patient-centered clinical decision support given the lack of standardization relating to how we encode data?*** We will discuss the challenges faced by authors, implementers and evaluators of CDS implementations by considering the following example of a CDS intervention by Adam Wright et al in the NIH-funded Improving Quality by Making an Accurate Problem List in the Electronic Health Record (EHR) (IQ-MAPLE) study. [12] In IQ-MAPLE, the investigators designed CDS interventions in the EHRs of four study sites to alert physicians when a candidate problem (e.g., Asthma, Hypertension, Hyperlipidemia) was detected that was missing from the patient's problem list (i.e., absence of structured input of diagnosis codes/terms to specify the key condition of interest). The clinician would then be able to accept the alert and add the problem, override the alert, or ignore it entirely. The investigators conducted a randomized trial and evaluated the effect of the problem list alert on three endpoints: alert acceptance, problem list addition rate and clinical quality.

In IQ-MAPLE, a team of clinical experts and informaticians designed and validated a series of problem inference algorithms, using rules-based techniques on structured data in the EHR and natural language processing on unstructured data. Then, they created CDS rules for suggesting conditions to add to a patient’s problem list that may have included:

- queries for the presence or absence of a diagnosis code (e.g., ICD-10CM, SNOMED CT® value sets by key condition) included in a patient’s problem list or encounter diagnosis.
- queries looking for currently active medications (e.g., RXCUI value sets by medication classes) in the patient’s record.
- queries for lab values (e.g., LOINC® value sets) that are within a specified range.
- various combinations and compound queries made up of the aforementioned sub-queries.

Even though the CDS rules and value sets in the IQ-MAPLE study were created centrally, there would have inevitably been variation in the implementations of the rules against clinical data at the four study sites. A report produced out of the collaboration between the Office of the National Coordinator for Health Information Technology (ONC) and the National Academy of Medicine (NAM) stated that there are at least four important technical challenges to sharing and therefore standardizing implementations of CDS content: (1) insufficient standardization of patient data representation; (2) insufficient standardization of

CDS knowledge representation; (3) insufficient standardization of CDS integration mechanisms; and (4) a need to align with broader standardization initiatives. [13]

Fundamentally, the representation and usage of clinical data and CDS knowledge across the four IQ-MAPLE study sites would have varied. One of the reasons that CDS interventions are difficult to implement between health care systems is because different EHR systems and health care systems utilize different underlying patient data models and CDS integration mechanisms. Even different instantiations of use of the same EHR systems differ in how they represent patient data. The ONC and NAM report stated that "[b]ecause CDS relies on inferencing using patient data, this heterogeneity in patient data representation poses an immense obstacle to sharing CDS." [13] In IQ-MAPLE, there were likely vast variations in the EHR user interfaces for how clinical data was entered in problem lists, representation of lab results, status and recording of currently active medications, and other miscellaneous clinical data inputs in patients' encounter notes.

In addition, there were likely variations in the usage of the value set and terminology content at the four study organizations. Therefore, there may have been discrepancies in how the CDS rules were triggered when they were deployed. For example, perhaps physicians at one of the study sites had been trained to use only diagnosis codes that align with Hierarchical Condition Category (HCC) codes in Centers for Medicare and Medicaid Services's (CMS) risk-adjustment model. These physicians would not have used any other diagnosis codes that may have existed in the IQ-MAPLE authored value sets for the CDS alerts. The other three study sites may not have operationalized such specific workflows, thereby reducing the standard representation of the IQ-MAPLE CDS alert implementations between the different medical centers.

The following challenges plaguing CDS implementations were described in a report produced out of the collaboration between the ONC and the National Academy of Medicine. [13]

1. Various pathways for implementation of CDS within different health care organizations
2. Lack of standards and incentives to use and improve CDS
3. Poor data quality
4. Gaps in the evidence

These challenges are due in part – according to the summary of Kawamoto's commentary in the ONC and NAM report – to a lack of clear standards for CDS content representation: "standards are not always defined clearly enough, so a developer will make a decision that enables content to work within [test] systems...but are not scalable nationally." [13] Consequently, there are vendor-specific solutions and organization-specific solutions that exist with "either a laborious configuration of external licensed content or a laborious reinvention of the wheel as the organization creates its own content." [13] Instead of creating a knowledge representation based on a standardized clinical data representation, current efforts are focused on creating and re-creating one-off "solutions". Even the latest CDS content standards, including Clinical Quality Language (CQL), CDS Hooks, and OpenCDS have yet to achieve "the necessary level of detail in the standards and how they are applied to clinical decisions." [13]

Therefore, one of the overarching challenges of standards that aim to make CDS shareable and interoperable is that there is currently not a robust way to associate rules in knowledge-based systems with other dependencies in clinical data representation systems to ensure proper operation. Current CDS standards are silent on the notion of identifying a safe configuration of dependencies between (a) the expression-logic for rules-based CDS techniques, (b) the value sets with codes and terms to define clinical concepts of interest contained in the CDS rules, and (c) the variability of how clinical data within the value sets and rules are inputted, modeled, and stored in data repositories.

These challenges have been explored by Wright et al when they studied CDS functionality at Brigham and Women's Hospital and illustrated ways in which clinical decision support systems malfunction and identified patterns of such malfunctions. [14] As a part of this study, a survey of 29 Chief Medical Infor-

mation Officers (CMIOs) showed that 93% of CMIOs experience CDS system malfunctions, and two-thirds experienced the malfunctions at least annually.

- One such malfunction was described as involving **inappropriate dependencies between and amongst the EHR system, CDS system, and other external systems** (e.g., lab information systems) . For example, "an alert for monitoring thyroid function in patients receiving amiodarone stopped working when an internal identifier for amiodarone was changed in another system." [14]

- Wright et al also found that **inappropriate configuration of dependencies perpetuated mistakes in underlying databases and value set management**: "a malfunction in an external drug classification system caused an alert to inappropriately suggest antiplatelet drugs, such as aspirin, for patients already taking one". [14]

- Thirdly, Wright et al wrote about how **inappropriate dependencies on EHR software caused numerous spurious alerts to fire**. [14]

3.3. Monitoring CDS - Design & Testing Considerations

As described above, Wright et al learned that Brigham and Women's Hospital did not have a system to track the siloed components of their EHR and CDS systems, nor did they have a process for tracking changes to the CDS rules, logic, and terminology implementations that were tied to other dependencies upstream or downstream in the implementation and process flow. Therefore, in IQ-MAPLE, the investigators tried to keep a closer eye on the design and functionality of CDS tools, including the background work required to update and maintain these complex systems.

To test the validity of their IQ-MAPLE CDS alert implementations, each study site organization might have built a testing environment to implement the CDS rules to detect whether each suggestion of a condition to add to a patient's problem list was "appropriate" or not. Such a testing environment would allow the CDS alerts to "silently" fire after they were built. In other words, the alerts were built and set to fire on patients in the back-end of the systems. End-users would NOT receive alerts at this stage. The alerts would "silently" fire for two weeks or some other agreed upon trial period. Then, the implementers would generate the list of patients for whom the silent alerts fire.

Next, basic face-validity would be performed upon perusal of the patient lists for whom the alerts silently fired. For a condition with a high prevalence like hypertension, an implementer may not be surprised to see hundreds of alerts firing in a 2-week span in their hospital, clinic, or medical center. Conversely, if the condition for a problem-list suggestion CDS rule is rarer, such as Sickle Cell Disease, then it would not be surprising to only see a handful of alerts fired in a 2-week silent run. If implementers thought that the count of alerts seemed off based on condition prevalence, then this could inform an analysis of the alert implementation and/or rules without having to do a more time-consuming chart-audit.

Next, patient charts for whom the alerts silently fire were abstracted to validate that the alerts fired on appropriate people. In this step, it may suffice to validate a smaller subset of patient records rather than validating hundreds of patient charts for whom alerts may silently fire. If the alerts were accurate at some threshold (e.g., 90%) based on the chart audit, then the alert could be marked as "appropriate" at a given institution. If inaccuracies arise in the chart audit during the silent firing testing phase, it may reveal errors in the implementation, or in the rules themselves prior to go-live deployment.

This sort of CDS testing environment would also allow for intra-organizational comparison of value set implementations or to assess the impact of inter-organizational updates to standard clinical terminologies over time. It could also be used to detect changes to CDS expression logic or rule changes and study the impact on the clinical data prior to deployment to better understand the impact of proposed updates.

3.3.1. Metrics for Monitoring CDS Implementations before and after Go-Live Deployment

This section will describe quality metrics for monitoring CDS performance. The ONC and NAM report highlighted the impetus for measuring whether CDS interventions are working: “ To optimize CDS and increase adoption and acceptance, it will be critical to determine which interventions are firing at the appropriate times and are then accepted by the clinical care team and patients and changing care for the better. This capability will be important at both the local and national scale if the goal is to reduce the burden on providers and health systems to each identify important lessons on their own." The following table shows examples of measures to determine the impact of CDS interventions. [14]

Table 3.1. Examples of Measures Commonly Captured to Measure the Effects of CDS Interventions

Measure	Examples
CDS Satisfaction, Usage, and Usability	• Usability assessments from end-users, end-user feedback, use of CDS from logs
Workflow Impact and Efficiency	• Time to complete work tasks before and after CDS, e.g., direct order entry, medication turn-around time
CDS Use by Clinicians	• Alert use, rate of alerts firing alert overrides • Number of times CDS alerts happen: (e.g., absolute counts, central tendency, percent change over time)
Healthcare Services Utilization and Efficiencies	• Reductions in unnecessary or inappropriate laboratory test orders
Costs	• Resource management,medication (number, type, class) and laboratory test costs
Unintended Consequences (Includes All Measure Types Above)	• Alert fatigue, overrides of serious alerts, adverse events due to CDS
Care Processes, Adherence to Guidelines	• Adherence to clinical guidelines; time to ordering of important medications
Patient Safety	• Error reports, adverse events, transfers to ICU, death, medication prescribing errors
Patient Outcomes	• Disease management related to adoption of guidelines (e.g., blood pressure control, lipid levels, HBA1c levels), hospital lengths of stay, rehospitalizations

3.3.1.1. Signs of an Effective CDS Roll-Out

Health IT.gov published a how-to manual for healthcare organizations to monitor CDS rollout plans and included the following criteria: [15]

- All end-users were adequately trained to use the intervention
- End-users felt the trainings were well-timed in relation to the roll-out
- End-users did not feel overwhelmed by the introduction of CDS

- End-users knew how to provide feedback and get support if needed
- Changes in workflow were smooth and improved care processes

3.3.1.2. Statistical Process Control Methods for CDS Anomaly Detection

A CDS malfunction (aka true positive anomaly) occurs when the CDS rule does not function as it was designed or expected to. The question that an evaluator of CDS interventions may ask is: ***Predict, given an expected number of events will happen, how many events will happen over time?***? When monitoring CDS count data over time, the underlying denominator likely will vary insignificantly. Therefore, statistical process control (SPC) charts can be created and the following tests can be performed: [16]

- Test #1 - The presence of a single point outside the control limits using the threshold 3*standard deviation.
- Test #2 - Two of three consecutive points are more than 2 standard deviations from the average line and both on the same side of the average line.
- Test #3 - Eight or more consecutive points on the same side of the average line.
- Test #4 - Six or more values steadily increasing or decreasing.

SPC anomaly detection can be attempted on time points for various time scales (e.g., weekly and monthly scale). To determine the characteristics and performance of SPC detection methods sensitivity, specificity, precision and the F measure can be determined.

3.4. Best Practices for CDS Knowledge Management and Deployment

As aforementioned in the section “Introduction to Clinical Decision Support”, the AMIA CDS Roadmap Development Steering Committee describes three pillars for realizing the promise of CDS: (1) Best Knowledge Available When Needed, (2) High Adoption and Effective Use, and (3) Continuous Improvement of Knowledge and CDS Methods. [1]

Given our discussion of challenges that plague CDS implementations, we propose a fourth pillar to be explicitly added to this framework:

- **Standardization Related to how we Encode and Represent Clinical Data**

  The underlying clinical data that feeds into CDS tools, interventions, and deployments must be represented, version-controlled, and encoded in a consistent, comprehensive, and systematic way.

3.4.1. Best Practices for CDS Knowledge Management

Below are some suggestions for Best Practices for CDS Knowledge Management: [17]

- Implement a clear, standard process for submission, review, evaluation, prioritization, and creation of all new CDS
- Maintain an up-to-date inventory of all CDS, including type (e.g., alert, order set), owner(s), dates of creation, dates of review, sources of evidence, clinical areas affected, and short description
- Manage terminologies and value sets using formal processes

- Periodically review the clinical evidence and assertional knowledge underlying the CDS rules and update as needed
- Use a formal software change control process for all CDS updates
- Enable review of the logic for CDS rules in human-readable format by clinical end-users (e.g., in a portal or repository)

3.4.2. Best Practices for CDS Deployment

Below are some suggestions for Best Practices for CDS Deployment: [17]

- CDS Deployment should use a process where changes to value set terminology codes made by Standards Development Organizations (SDOs), value set developers, or by ancillary department internal systems are communicated and pushed to CDS authors, implementers, and evaluators to be analyzed for impact before the changes are made.
- CDS Deployment should employ a process where changes to attribute values (e.g., units of measurement) are communicated and pushed to CDS authors, implementers, and evaluators to be analyzed for impact before the changes are made.
- CDS Deployment test and deploy EHR vendor patches and upgrades in a timely manner.
- CDS Deployment should inform users of significant CDS changes.
- CDS Deployment require IT staff to use automated tools to migrate CDS rules between EHR system environments (e.g., test and production).

3.4.3. Ten Commandments for Effective CDS

Bates et al published the *Ten Commandments for Effective Clinical Decision Support: Making the Practice of Evidence-based Medicine a Reality* with "the goal…to present generic lessons from [their CDS] experiences that may be useful to others, including informaticians, systems developers, and health care organizations." [18] The paper includes the following Ten Commandments for Effective CDS:

1. **Speed is Everything** - "[T]he speed of an information system is the parameter that users value most. If the decision support is wonderful, but takes too long to appear, it will be useless."
2. **Anticipate Needs and Deliver in Real Time** - "[A]pplications must anticipate clinician needs and bring information to clinicians at the time they need it."
3. **Fit into the User's Workflow** - "Understanding clinician workflow, particularly when designing applications for the outpatient setting, is critical."
4. **Little Things Can Make a Big Difference** - Usability matters a lot. CDS must be understandable, useful and encompass the needed functionality. Furthermore, CDS should be easy to learn, efficient to use, easy to remember, subjectively pleasing, and contain few (or no) errors.
5. **Recognize that Physicians Will Strongly Resist Stopping** - Bates et al "found that physicians strongly resist suggestions not to carry out an action when [they did] not offer an alternative, even if the action they are about to carry out is virtually always counterproductive."
6. **Changing Direction Is Easier than Stopping** - CDS can be a powerful tool for changing physician behavior. Bates et al were "especially effective when the issue at hand is one attribute of an order the physician probably does not have strong feelings about, such as the dose, route, or frequency of a medication or the views in a radiographic study."

7. **Simple Interventions Work Best** - "If you cannot fit a guideline on a single screen, clinicians will not be happy about using it."

8. **Ask for Additional Information Only When You Really Need It** - "[T]he likelihood of success in implementing a computerized guideline is inversely proportional to the number of extra data elements needed."

9. **Monitor Impact, Get Feedback, and Respond** - "Carefully evaluate and prune the CDS knowledge base."

10. **Manage and Maintain Your Knowledge-based Systems** - Maintaining the knowledge within the system and managing the individual pieces of the system are critical to successful delivery of decision support.

3.5. Historical Context for Representing the Expression Logic of Clinical Decision Support

While there have been advancements over the past few decades in implementing clinical data standards (e.g., SNOMED CT®, LOINC®), there is still room to improve portability of CDS implementations across healthcare organizations. Different health care institutions may increasingly have their clinical data encoded according to standards-based terminologies, but each site will still require human intervention and hand-crafted implementations of computerized CDS, including patient safety alerts and health maintenance reminders intended to improve population health. One implementation of a CDS alert at a given institution is not completely transferrable to another institution, even if the organization is using the same Health IT system. Analysts at each organization will have to modify the underlying query so that it is computable against their respective clinical database structure. Furthermore, not all clinical concepts are recorded and stored in the same way in different EHR implementations; what may be structured in one system may be free text in another. While the Health Quality Measure Format (HQMF), Quality Data Model (QDM), and Clinical Quality Language (CQL) are the more recent efforts to improve standard representations of CDS expression logic, efforts date back to the mid 1970's when early implementers of computer-based clinical information systems were first recognizing the value of computer-based decision support into their designs.

Notably, Clem McDonald's work on the Regenstrief Medical Record System exemplifies important early work in pseudocode logic expression. McDonald realized that the number of CDS reminders and alerts would quickly increase, so rather than hand-crafting each rule into computer code with programmers, he created one of the first CDS rule languages called CARE. [19] The CARE language allowed clinical experts and those without programming expertise to structure if-then logic alerts using a flexible scripting language that could be interpreted by programmers to implement against the patient record system. As computerized EHRs continued to spread to other academic medical centers in the years that followed, it became clear that a standard way to replicate the expression logic of CARE-style if-then decision rules would be needed. In the late 1980s, informaticists at Columbia led an important initiative to standardize CDS scripting language and created the Arden Syntax or Medical Logic Modules, the goal of which was to encode if-then-else rules in a standard format that could be computed against different EHR systems, regardless of the location or specific vendor. Arden Syntax logic modules were novel in that they consisted of standard sections called 'categories', and each category contained several 'slots'. For instance, the 'logic' slot contained the actual clinical logic of a rule, and the 'action' slot defined the message that the rule would display to the clinician-user. Modern EHRs often still use this framework even if the full Arden Syntax is not used: when a clinician's workflow reaches a trigger point, then a rule in the system is fired, and evaluates the clinical logic attached to the trigger point. [19]

By the mid 1990's, CDS rules using the Arden Syntax began to spread to numerous commercial systems, however dissemination was limited in that rules written in one facility would not run against any other system. While the 'logic' slot contained machine-executable if-then-else code, there was also a 'curly

brace' part of the syntax that only contained a human-readable textual description of the database process and actions necessary for the rule to access clinical data in the EHR. This required human-interpretation and hand-crafting at each specific site and this challenge was referred to as the "curly brace problem". [19] This challenge to achieve portability across environments has persisted throughout the 1990s to 2000s to the current day. These challenges were only worsened when guideline-based techniques were introduced attempting to separate clinical problems into a series of linked clinical decisions. There were some notable efforts such as Guideline Interchange Format (GLIF), PROforma, SAGE, and GEM, which aimed to incorporate a guideline's logic into the executable part of decision logic, however these languages suffered due to a lack of maturity of standards to integrate the guideline engines into EHRs directly. [19][ ]

In 1998, HL7 found the "curly brace" problem to be unsolvable by the Arden approach and began efforts to create expression logic standards based on HL7 Version 3 Reference Information Model (RIM). One attempt was the GELLO Expression Language, which in theory was supposed to access and manipulate clinical data by common clinical entities; however RIM was not proven to be a very practical representation of the complexity of real-world data. Only a small number of vendors were successfully able to implement RIM-based EHRs and therefore the vision of GELLO and HL7 V3 efforts remained unproven. In 2013, HL7 replaced GELLO with "Event, Condition, Action" (ECA), an expression in XML data structures intended to abstract the representation of expression logic. Shortly thereafter, the standards community realized the benefit in aligning CDS logic expression with those of eCQMs, as the goals of CDS rules are often used to prompt clinicians to achieve improved clinical quality outcomes. Therefore, HL7 defined the Quality Improvement and Clinical Knowledge model (QUICK). QUICK and ECA have now been wrapped up into the Clinical Quality Language (CQL), which attempts to capture lessons learned from Arden, GELLO, and ECA.

An emerging HL7 International standard that might help with electronic processing of eCQM and CDS logic is CQL, a new specification that focuses on a common model for representing expression logic for CQMs and Clinical Decision Support. According to CMS' eCQI Resource Center, CQL will be used in all quality measure specifications in the future, will replace the Quality Data Model (QDM), and is intended to reduce the burden on implementers for consuming measure artifacts. CQL representations of eCQMs will replace the QDM pseudocode historically published in HQMF files; it aims to provide a human-readable, conceptual-level language to define eCQMs and clinical decision support independent of specific data models, such as the QDM or FHIR.

CMS is rapidly rolling out the CQL standard in its eCQMs and CDS for the 2019 reporting year. The goal of CQL moving forward is to use emerging Application Programming Interfaces like FHIR as a way to allow for more direct access to clinical data that does not require the overhead of RIM mapping. [20] The potential for FHIR and CQL in CDS and eCQM implementations remains to be seen, however, the community is optimistic.

3.6. Tools that Enhance CDS

CDS encompasses a variety of tools to enhance decision-making in the clinical workflow. In this section, we will define and discuss Standard Operating Procedures, Clinical Practice Guidelines, Clinical Pathways, Treatment Protocols, Order Sets, and KNARTs.

3.6.1. Standard Operating Procedures (SOP)

Standard Operating Procedures (SOPs) "are a specific set of practices that are required to be initiated and followed when specific circumstances arise. In clinical care, clinicians have historically been familiar with SOPs in specific types of restricted contexts. For example, emergency room physicians have SOPs for patients who are brought in an unconscious state; nurses in an operating theater have SOPs for the forceps and swabs that they hand over to the operating surgeons; and laboratory technicians have SOPs for handling, testing, and subsequently discarding body fluids obtained from patients."

Now that EHRs and electronic clinical data in some capacity are essentially ubiquitous in the United States, Health IT implementations often come with tools making it possible to achieve SOPs "into routine clinical practice; that is, not for special patients (e.g. those who are unconscious) or for special circumstances (e.g. clinical trials), but for every patient in everyday clinical care." [21]

3.6.2. Clinical Practice Guidelines

Clinical Practice Guidelines are systematically developed statements on medical practices that assist a clinician in making decisions about appropriate diagnostic and therapeutic healthcare services for specific medical conditions. These guidelines should be evidence-based and use research evidence along with clinical expertise and patient preferences in providing care. Guidelines are usually developed by authoritative professional societies and organizations. Guidelines provide clinicians and patients the recommendations for screening, diagnostic and therapeutic actions that are known or believed to favorably affect the health outcomes of patients. Guidelines are not meant to replace the clinical judgement of the individual provider or establish a standard of care. They are meant to be flexible and are only considered as recommendations. Where Guidelines are meant to be flexible, standards are a rigid set of criteria, meant to be followed under any circumstances. [21]

3.6.2.1. Examples of Guidelines

The Society of Nuclear Medicine & Molecular Imaging in collaboration with other professional society creates and hosts 'Procedure Standards' for a variety of comprehensive procedure guidelines describing how to perform medical and research procedures. [22]

Similarly, the American Academy of Family Physicians (AAFP) develops evidence-based clinical practice guidelines (CPGs), which serve as a framework for clinical decisions and supporting best practices. Clinical practice guidelines are statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence, and an assessment of the benefits and harms of alternative care options. CPGs should follow a sound, transparent methodology to translate best evidence into clinical practice for improved patient outcomes. Additionally, evidence-based CPGs are a key aspect of patient-centered care. [23]

AHRQ's Guidelines and Measures (GAM) provides users a place to find information about legacy guidelines and measures clearinghouses, 'National Guideline Clearinghouse' (NGC) and 'National Quality Measures Clearinghouse' (NQMC). [24] The NGC mission was to provide physicians and other health care professionals, health care providers, health plans, integrated delivery systems, purchasers and others an accessible mechanism for obtaining objective, detailed information on clinical practice guidelines and to further their dissemination, implementation, and use. The NQMC mission was to provide practitioners, health care providers, health plans, integrated delivery systems, purchasers and others an accessible mechanism for obtaining detailed information on quality measures, and to further their dissemination, implementation, and use in order to inform health care decisions.

3.6.3. Clinical Pathways

Clinical Pathways are one of the main tools used to manage the quality in healthcare concerning the standardization of care processes. They intend to reduce variability and clinical practice, thereby improving outcomes. Clinical pathways appeared as a result of the adaptation of the SOP documents used in industrial quality management whose goals are to improve efficiency in the use of resources and to finish work in a set time.

Clinical pathways incorporate evidence-based guidelines and protocols for common diagnoses, conditions and procedures into algorithms. These algorithms are used by the multidisciplinary care team in providing care to the patient.

Items addressed on the clinical pathway may include:

- patient assessment and monitoring,
- tests and procedures,
- treatments,
- consultations,
- medications,
- activity,
- nutrition,
- education,
- targeted length of stay,
- outcome criteria, and
- notification for deviations.

Standardizing treatments improves the continuity and coordination of care provided by all disciplines involved. This should result in greater quality of care and decreased costs.

3.6.3.1. Pathways vs SOPs vs Guidelines

Rao et al. provide definitions to help compare/contrast SOPs, guidelines, and clinical pathways:

"The terms SOPs, guidelines and [clinical] pathways are defined by different medical bodies. Furthermore, whereas clinical practice guidelines are systematically developed statements that assist decisions about appropriate health care for specific circumstances, SOPs are more specific than guidelines and are defined in greater detail. They provide a comprehensive set of rigid criteria outlining the management steps for a single clinical condition or aspects of organization.

Guidelines are rigorously developed using evidence-based medicine criteria and consist of two distinct components: the evidence summary and the detailed instructions for the application of that evidence to patient care. For the common health care provider, guidelines require local adaptation to suit local circumstances and to achieve a feeling of ownership, both of which are important factors in guideline uptake and use. SOPs, therefore, help bridge the gap between evidence-based medicine, clinical practice guidelines, and the local realities at the point-of-care." [25]

3.6.4. Treatment Protocols

Standardized treatment protocols decrease variability and improve the quality of clinical care by simplifying the treatment options, particularly in primary health care. Standard treatment protocols can be developed by preparing new treatment guidelines or by adapting or adopting existing national or international guidelines. [26] When embedded in electronic health records, treatment protocols can serve as clinical decision support at the point of care so no opportunities are missed to achieve control. [26]

3.6.5. Order Sets

Order sets are a group of related orders which a user can apply to a specified diagnosis or a particular period of time. Order sets reduce both time spent entering orders and terminal usage, helping to improve user acceptance of computer-based physician order entry. [27]

3.6.6. Knowledge Artifacts (KNARTs)

KNART is a Clinical Decision Support Knowledge Artifact and is a structured way of documenting the content/knowledge for three different types of CDS interventions: 1) event condition action (ECA) rule (e.g., clinical reminder), 2) order sets, and 3) documentation templates (VA has called them SMARTForms or PNCS forms in the past).

KNARTs are a standard HL7 format. While they are not the actual executable CDS interventions, they provide the information that a developer can take and then implement within an EHR. The main benefit to KNARTs is that you can share them with other healthcare organizations in a standardized manner that they can take and implement within their own EHR, if they choose.

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