Ontological Representation of Laboratory Test Observables: Challenges and Perspectives in the SNOMED CT Observable Entity Model Adoption

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Abstract. The emergence of electronic health records has highlighted the need for semantic standards for representation of observations in laboratory medicine. Two such standards are LOINC, with a focus on detailed encoding of lab tests, and SNOMED CT, which is more general, including the representation of qualitative and ordinal test results. In this paper we will discuss how lab observation entries can be represented using SNOMED CT. We use resources provided by the Regenstrief Institute and SNOMED International collaboration, which formalize LOINC terms as SNOMED CT post-coordinated expressions. We demonstrate the benefits brought by SNOMED CT to classify lab tests. We then propose a SNOMED CT based model for lab observation entries aligned with the BioTopLite2 (BTL2) upper level ontology. We provide examples showing how a model designed with no ontological foundation can produce misleading interpretations of inferred observation results. Our solution based on a BTL2 conformant formal interpretation of SNOMED CT concepts allows representing lab test without creating unintended models. We argue in favour of an ontologically explicit bridge between compositional clinical terminologies, in order to safely use their formal representations in intelligent systems.

Keywords: Biomedical ontologies and terminologies · LOINC · SNOMED CT · BioTopLite2

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1 Introduction

The emergence of Electronic Health Records has raised interoperability challenges in (i) the establishment of common data structures and (ii) the definition of semantic standards to represent clinical information. The representation of *in vitro* diagnostic observation (Table 1) in laboratory reports follows a global tendency by health care providers and public health institutions [1] towards two semantic standards, *viz.* the Logical Observation Identifiers Names and Codes (LOINC) terminology [2, 3] and the ontology-based clinical terminology SNOMED CT [4–6]. Whereas LOINC provides precise, compositional encodings of lab tests and other clinical observables, SNOMED CT provides codes for nominal and ordinal scale result values. For three years, the respective maintenance organisations, Regenstrief Institute and SNOMED International have worked together in order to elaborate a first representation of 13,756 LOINC tests (over a total of 79,000) as post-coordinated SNOMED CT expressions [7, 8]. The main advantage of this LOINC–SNOMED CT interoperation is to enable the representation of observation results (pairs of lab test observables with result values) within SNOMED CT, using its post-coordination mechanism.

Table 1. Definitions of main notions and examples of a naïve observation model.

Term	Definition	Example
Observable	a plan for an observation procedure to observe a feature (quality, disposition, or process quality) of an entity	*Non-invasive systolic blood pressure, measured on upper left arm.*
Lab test observable	*in vitro* diagnostic tests represented by LOINC or SNOMED CT concepts in the Observable Entity subhierarchy	*17279-1 Bacteria identified: Prid:Pt:Plr fld:Nom:Aerobic Culture*
Result value	immaterial, information-like outcomes of an action	*Present*, *Absent*
Observation	realization of an Observable yielding a Result value, typically described as a Observable – Result vale pair	

This article focuses on the use of SNOMED CT to describe lab test observables and observations. We present a hierarchical reorganisation of lab test observables computed by the ELK inference engine [9] and discuss their usability into observation context. We demonstrate that hierarchical lab test structures combined into naïve ad-hoc observation models raise misleading interpretations. Motivated by unintended results, we propose a new model to represent observation entries, compatible with the SNOMED CT lab test observables formalization under the biomedical upper level ontology BioTopLite2 [10].[1]

[1] In the following, we will abbreviate BioTopLite by BTL2 and SNOMED CT by SCT. In lower case, these acronyms will also be used as namespace identifiers.

This article is organized as follows. Section 2 presents current resources and the classification method used. Section 3 presents our results. In the last section, we discuss the results obtained and give an outlook to further work.

2 Materials and Methods

2.1 Terminologies and Ontologies

LOINC is a terminology created in 1994 by the Regenstrief Institute to represent clinical and lab tests [2, 3]. Its version 2.54, used in this study, describes 79,000 tests, of which approximately 50,000 are lab tests. Test models in LOINC are defined by six main dimensions that represent information about protocols (Analyte, Method, Time and System), together with the type of result values expected (Scale and Property). Test descriptions can be refined by the addition of three optional items of information (Challenge, Divisor and Adjustment).

SNOMED CT (SCT) is an increasingly ontology-based clinical terminology created in 2002 to formally represent the wide range of terms used of the clinical domain [5]. It is maintained by SNOMED International (formerly IHTSDO), and distributed in a relational file format (RF2) [6], from which an OWL EL ontology can be programmatically derived [4]. SNOMED CT's January 2016 international release is constituted by around 300,000 concepts, thematically arranged by 18 mostly disjoint subhierarchies. A SNOMED International working group has, since then, invested considerable effort in improving SCT's *Observable Entity* subhierarchy by ontology patterns [11], which sets clinical and lab tests description on formal-ontological grounds and allows enough flexibility to mimic the granularity of LOINC. The new Observable entity model was introduced in the international SCT release in January 2017.

The LOINC – SCT resource described in this paper is the third technical preview release provided by Regenstrief and SNOMED International [7, 8] in April 2016, using the SCT January 2016 release, as an outcome of an interinstitutional cooperation agreement signed in July 2013. It represents the representation of 13,786 LOINC (28% of lab) codes into SCT post-coordinated expressions using Observable Entity ontology patterns. The LOINC – SCT alignment release is distributed in three formats: RF2, OWL and Excel ("Human Readable"). In this study we used the OWL format.

BioTopLite2 (BTL2) is a top-domain ontology [10] that intends to address the need for clear-cut upper-level classes (55) and relations (37), thus improving and facilitating ontology engineering and inter-operation. A preliminary bridge between SCT and BTL2 has been proposed in 2015 [12], addressing the problem that SCT's basic ontological assumptions are partly hidden in the documentation and partly underpinned by OWL examples scattered across publications.

2.2 Lab Test Observable Classification

The reason for the automatic classification of LOINC concepts based on SCT expressions was to use description logics inference in order to add new subclass links

to the hitherto flat LOINC structure. It was performed on the OWL file of the third release of the LOINC – SCT resource as described in the previous paragraph. The classification process is composed of two steps:

- Firstly, the OWL version of the SCT January 2016 international release is imported.
- Secondly, the ELK reasoner [9], which computes description logics inferences on OWL EL with a good scalability behaviour, is used to reclassify the merged ontologies.

3 Results

3.1 ELK Classification Metrics

We first observed that 45 lab test observables were inferred as pairwise equivalent. The ELK inference engine also infers subsumption relationships for half (6,789) of the SCT post-coordinated expressions that represent LOINC codes. Among them, we observed that 16.6% were classified into poly-hierarchies. The resulting taxonomy of lab test observables had an average depth of 1.5, with a maximum of five levels below the top concept *363787002 | Observable entity*. We distinguished two reasons of the obtained subsumption: definition increment (31% of inference) and definition refinement (78%).

▼ '31718-0 Astrovirus Ag:ACnc:Pt:Stool:Ord' **(*A*)**
'7810-5 Astrovirus Ag:ACnc:Pt:Stool:Ord:EIA'

'*7810-5* ***Astrovirus Ag:ACnc:Pt:Stool:Ord:EIA***' equivalentTo **(*B*)**
sct:*Observable entity* and
sct:Component some sct:*AstrovirusAntigen* and
sct:Scale type some sct:*OrdinalValue* and
sct:Time aspect some sct:*SinglePointInTtime* and
sct:Property type some sct:*ArbitraryConcentration* and
sct:Inheres in some sct:*GastrointestinalTractMaterial* and
sct:Direct site some sct:*StoolSpecimen* and
sct:Technique some sct:*EnzymeImmunoassayTechnique*

Fig. 1. ELK reclassification of a LOINC post-coordinated concept: definition increment. (A) Hierarchical relation inferred by ELK; (B) *'7810-5 Astrovirus Ag: ACnc:Pt:Stool:Ord:EIA* definition (the restriction added to the '31718-0 *Astrovirus Ag:ACnc:Pt:Stool:Ord*' definition is underlined).

We understand by "definition increment" computed subclass inferences entailed by additional restrictions in the formal definition of more specific lab test observable concepts (Fig. 1). For instance definition of the post-coordinated concept *'7810-5 Astrovirus Ag:ACnc:Pt:Stool:Ord:EIA*' specifies the technique used (underlined in Fig. 1B, *viz.* lab test using enzyme immunoassay technique), whereas the definition of *'31718-0 Astrovirus Ag:ACnc:Pt:Stool:Ord* ' does not (lab test using any technique). We observed that 91.3% of the definition increment subsumptions were caused by the

addition of the technique information to the subtest definition, in this particular case, the technique enzyme immunoassay.

By "definition refinement" we mean classification inferences entailed by hierarchical relationships between existing SCT concepts, used in the same part of lab test observables definitions (Fig. 2). For instance the LOINC post-coordinated concept *'17279-1 Bacteria identified:Prid:Pt:Plr fld:Nom:Aerobic Culture'* is computed as a subclass of *'618-9 Bacteria identified:Prid:Pt:Plr fld:Nom:Culture'*, because the concept *Aerobic culture* is a child of *Culture* (i.e. any culture) in SCT. We observed that such definition refinement assertions were mainly (4,878 - 90.1%) due to concepts representing the *Component* dimension in LOINC code, i.e. the specific component of the material analyzed like a bacteria of pleural fluid in this case.

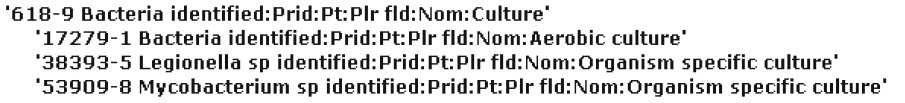

Fig. 2. ELK classification of organism culture in pleural fluids sample lab test observables, example of definition refinement.

3.2 Lab Test Classification Issue

In ontologies, the subsumption relationship (**rdf:subClassOf** [13]) is transitive (1) and expresses that every individual member of subsumed class is also member of the corresponding superclass(es) (2).

$$c_1 \textbf{ rdfs:subClassOf } c_2 \wedge c_2 \textbf{ rdfs:subClassOf } c_3 \Rightarrow c_1 \textbf{ rdfs:subClassOf } c_3 \quad (1)$$

$$c_1 \textbf{ rdfs:subClassOf } c_2 \Rightarrow \text{Instance}(c_1) \subset \text{Instance}(c_2) \quad (2)$$

Figure 2 illustrates the classification of observables on organism cultures from pleural fluids. From a logical perspective, the classification is consistent. Indeed, *Aerobic culture* is a kind of *Culture*, as well as the assertion that a lab test for an anaerobic bacteria culture ('*17279-1 Bacteria identified:Prid:Pt:Plr fld:Nom:Aerobic Culture*') is more specific than a lab test applying any bacteria culture test technique ('*618-9 Bacteria identified:Prid:Pt:Plr fld:Nom:Culture*'). In a laboratory report context, lab test observables described by LOINC are used to represent observation entries (see Table 1). In the next section we will present how the lab tests classification can mislead users in the interpretation of inferred observation statements.

Problem Statement. In this section we consider a naïve interpretation of *in vitro* diagnostic observations (Table 1 and Fig. 3A), in which an observation is expressed by a direct relationship between a lab test observable and test result value, linked by the relation **hasResultValue**. In the following example, i_1 and i_2 are two instances of the observation result concept (Fig. 3B, C) representing the lab test observable *'17279-1 Bacteria identified:Prid:Pt:Plr fld:Nom:Aerobic Culture*' on pleural fluid, together with the result values *Present* and *Absent*.

First, we consider the i_1 observation result pattern representing the presence of bacteria in aerobic culture condition from pleural fluid. Under the interpretation of i_1 being an instance of *'17279-1 Bacteria identified:Prid:Pt:Plr fld:Nom:Aerobic Culture*' and **hasResultValue** some *Present* (literally the ***Presence*** *of bacteria in* ***aerobic*** *culture in pleural fluid).* i_1 is inferred as being also an instance of the expression *618-9 Bacteria identified:Prid:Pt:Plr fld:Nom:Culture*' and **hasResultValue** some *Present* (***Presence*** *of bacteria in* ***some*** *culture of pleural fluid)* because i_1 is also an instance of the '*618-9 Bacteria identified:Prid:Pt:Plr fld:Nom:Culture'* test (Eq. 2, Fig. 2). In this assertion the *some* constructor is inherited from the formal definition and thus is not explicitly stated in the observation. Nevertheless, it plays a key role in the interpretation of the inferred observation. This explains why a naïve interpretation would be misleading, because the existentiality notion (*i.e.* ∃) would be intuitively ignored, as we will see later. As long as the i_1 observation is positive ("presence"), the entailment of "*presence of bacteria in pleural fluid culture*" seems plausible and straightforward.

Observation pattern equivalentTo sct:*ObservableEntity* and **hasResultValue** some *Value* ***(A)***

i_1 Type: *'17279-1 Bacteria identified:Prid:Pt:Plr fld:Nom:Aerobic Culture*' and **hasResultValue** some *Present* ***(B)***

i_2 Type: *'17279-1 Bacteria identified:Prid:Pt:Plr fld:Nom:Aerobic Culture*' and **hasResultValue** some *Absent* ***(C)***

Fig. 3. Simple model of observation entry pattern (A) and two examples of instances.

Contrary to i_1, the instance i_2 of the observation class represents a negative assertion (***Absence*** *of bacteria in pleural fluid* ***aerobic*** *culture*) and can produce a misleading interpretation due to the subsumption of the observation result. The individual i_2 is also an instance of '*618-9 Bacteria identified:Prid:Pt:Plr fld:Nom:Culture'*, equivalent to '*618-9 Bacteria identified:Prid:Pt:Plr fld:Nom:Culture*' and '**hasResultValue**' some *Absence* (literally "***Absence*** *of bacteria in* ***some*** *culture of pleural fluid sample").* In our example, this means that the statement "***Absence*** *of bacteria in some culture of pleural fluid sample*" is not sufficient to infer the general statement "***Absence*** *of bacteria in pleural fluid culture*". In other words, this would not contradict that in another pleural fluid culture, e.g. for anaerobic bacteria, the finding is positive.

This example shows that the 'naïve' representation of the observation model (Fig. 3A), as it might be interpreted by non-ontologists, misleads the interpretation of inferred lab test observation results. The phenomenon, exemplified regarding *in vitro* diagnostic observations with binary result values (*Present*, *Absent*), can easily be generalized to ordinal and quantitative result values. In the next section we propose a solution to this issue by formalizing observation entry and lab tests with general categories proposed by the BTL2 upper-level ontology [10].

Lab Test Redefinition with BioTopLite2. Lab tests as described in LOINC, as well as in SCT under *Observable Entity* are meant to be representations, i.e. information about processes but not the processes themselves. The Regenstrief Institute's characterisation of LOINC codes as "universal names and ID codes for identifying laboratory and clinical test results" [14] suggests exactly this. This distinction is also justified by the fact that a given LOINC code can be assigned to different *in vitro* diagnosis products from different manufacturers, each with a different laboratory process.

The distinction between information and process is materialized in BTL2 by the disjointness between the categories *btl2:InformationObject* and *btl2:Process*. The characterization of lab test observables as being information objects (*btl2: InformationObject)* and not processes sheds light on misleading interpretations of the observation pattern as exposed in the previous section (Fig. 3A). That lab test observables are information objects in the sense of BTL2 is fully coherent with the fact that they are complemented by observation result values. Result values are (immaterial, information-like) outcomes of an action (in our example represented by the lab test processes proper). The word "observation" (Table 1), in this context, is rather confusing than helpful, as it alludes, first, to the classical diagnostic observation of a patient: a clinician observes the skin of a patient (observation action) and concludes that it is pale (observation result value). This value is documented in the patient record, next to the entry "skin colour" (lab test observable). The summation of the two information entities "skin colour" and "pale", makes the information complete.

In parallel, a machine "observes" (actually measures) a blood sample for haemoglobin. The outcome "9 mg/ml" (observation result value), is, in this case, more precisely a piece of information produced by a machine, which completes the lab observable "Haemoglobin concentration in blood" (again, an information object). Both composite information objects, *viz.* "Skin colour: pale" and "Haemoglobin concentration in blood: 9 mg/dl" then represent some medical condition like *Anaemia*. Note that this does not mean that there is always an instance of anaemia, because the results of observations and measurements, as such, bear the possibility of being non-referring, e.g. due to the clinicians' diagnostic error, due to inappropriate light conditions, or due to a technical error in the machine.

The discussed implausible inference also highlights difficulties in interpreting ontologies for practical applications. A clarification of the intended meaning, and, in consequence the prevention of implausible interpretations, can be achieved by reference to an upper-level ontology like BTL2, as we have demonstrated. We will therefore propose a consistent modelling pattern for representing observables extracted from laboratory reports, placing SCT and LOINC under BTL2. Model requirements and the definition of the main concepts are presented in the following section.

3.3 Representation of Observation Using BTL2

The above issue is addressed by proposing a new SCT approach to represent laboratory observables called "Observation entry". This model intends to complete SNOMED International's work on the formalization of lab test observables [11] rather than competing with it. Indeed, SNOMED International started to address this issue

Observation equivalentTo *btl2:InformationObject* and **(A)**
btl2:hasComponentPart exactly 1 *LabTestObservable* and
btl2:hasComponentPart some *ResultValue*

sct:*ObservableEntity* subClassOf btl2*:InformationObject* **(B)**

LabTestObservable subClassOf sct:*ObservableEntity* **(C)**

ResultValue subClassOf btl2:*InformationObject* **(D)**

XResultValue equivalentTo Result Value and **btl2:represents** only sct:X **(E)**

Fig. 4. Observation model main class definitions. *XResult* according to [15].

especially with the Observables working group, which formalized an ontology pattern for lab test observables within the *Observable Entity* hierarchy and proposes a formalization of the *result value* (named *Observation Result* in the SCT document) according to existing concepts and relations in SCT [11]. Our contribution to the conceptualization of observation is to offer a different point of view using BTL2 as ordering principle.

We define *Observation* (Fig. 4A, Table 1) as an *Information object* composed by a lab test observable and associated result value information: it is formalized by the mereological sum (**btl2:hasComponentPart)** of the *Lab Test Observable* (a specific type of information object) and the test result value (*Result value*). These definitions, in addition of being consistent with BTL2, solve misleading interpretations. Indeed, as observation result concepts (Table 1, Fig. 4A) are no longer subsumed by lab test observable concepts, the entailment of instances due to the **rdfs:subClassOf** definition will no longer occur. The *Lab test observable* concept (Fig. 4C) is an *Observable Entity* post-coordinated expression (Fig. 4B) as defined in the LOINC–SNOMED CT harmonization resource. *Lab test observable* is modelled as indirectly subsumed by *btl2:InformationObject*.

The *Result Value* concept (Fig. 4D) is instantiated by information produced by observation or analysis processes. In laboratory reports, we distinguish between two kinds of results and each has its own formalization: Literal result values are alphanumeric symbols or concatenations thereof, which form numbers or strings of characters like DNA sequences. *Literal Result Value* is a new concept linked to *rdfs*: *Literal* with the **hasValue** datatype property. It is disjoint from *Result Value*. We refrain from any further ontological account of literal results, especially numbers, due to the inherent intricacy of the ontology of mathematical objects, and the lack of relevance for most use cases. Opposed to *Literal result values*, *X result values* (Fig. 4E) are "conceptual" outcomes, which correspond to concepts in ontologies like SCT. Interestingly, *X result values* cannot be directly represented by the terminology codes. Considering *3092008 | Staphylococcus aureus,* this SCT concept can be used in SCT to define a disease (*i.e. 441658007 | Pneumonia caused by Staphylococcus aureus*) as well as in lab reports to point to the result of a bacteria identification test. Whereas in the first case, the definitions implies that *Staphylococcus aureus* instances, i.e. real bacterial organisms (under *btl2:Material object*), in the case of lab reports the target concept must be *Information object*, according to our stipulations. Because *material*

object and *information object* are disjoint in BTL2, we here need another way to refer to *Staphylococcus aureus*. So we propose to formalize *X result values* (Fig. 4E) as information objects linked to a SCT concept (not an instance) by the BTL2 relation **represents**, using the quantifier "only", according to the proposal in [16]. In our previous example, this means that the concept *Staphylococcus aureus* will not be directly used in the Observation Entry model to express *Lab test result values*. We would therefore rather create a new post-coordinated concept which follows the *X Result Value* pattern [15], cf. Fig. 4E.

4 Conclusion

This paper elaborates on the representation of laboratory observables with SNOMED CT. We first studied the LOINC – SNOMED CT harmonization resource, which proposes a representation of LOINC lab tests by post-coordinated SNOMED CT expressions and observed that the classification of lab test observables was enhanced due to a formal representation in OWL-EL and the SNOMED CT concept hierarchy. A previous study [16] on the LOINC – SNOMED CT resource had also demonstrated benefits of SCT to enhance lab test queries.

We then focused on the formalization of lab test observables. We analysed a typical pattern representing information stored in laboratory reports and demonstrated how it might be interpreted by lab staff. We showed how naïve interpretations of lab test observation results is misleading because they blend the meaning of represented and representing entities. An implementation of this naïve model in clinical decision support system could, in the worst case, infer wrong observation results and affect patient safety if included in a medical decision support pipeline.

We finally formalized a new observation model constrained by the BioTopLite (BTL2) upper level ontology. Bridging the observation model to BTL2 clarifies the intended meaning of lab tests and observations. This shows the normative value of a strict upper level ontology, which would also be helpful for guiding the development of other ontologies like SNOMED CT. By that means, the ontology could evolve in a more principled way, avoiding the risk of competing ontological commitments [17]. SNOMED CT would thus gain more reliability in coding clinical information like lab results, which impacts on decision support and data analytics use cases. Standardization of patient data, especially with SNOMED CT, opens up new opportunities for implementing new clinical decision support tools putting *in vitro* diagnostic observation into a global patient context. In clinical microbiology [18], experts systems (as Vitek2 AES [19]) or ontologies [20] propose therapeutic corrections and antibiotic stewardship implementing rules extracted from guidelines. A principled observation model addressing the representation of *in vitro* diagnosis, compatible with a worldwide clinical terminology like SNOMED CT would therefore be a cornerstone for reliable decision support. Further steps will be to enhance and evaluate its capacity to perform decision support based on *in vitro* diagnostic data.

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