Andreas Bietenbeck*, Martin Boeker and Stefan Schulz

NPU, LOINC, and SNOMED CT: a comparison of terminologies for laboratory results reveals individual advantages and a lack of possibilities to encode interpretive comments

https://doi.org/10.1515/labmed-2018-0103
Received July 31, 2018; accepted September 17, 2018; previously published online October 25, 2018

Abstract

Background: Terminologies facilitate data exchange and enable laboratories to assist in patient care even if complex treatment pathways involve multiple stakeholders. This paper examines the three common terminologies *Nomenclature for Properties and Units* (NPU), *Logical Observation Identifiers Names and Codes* (LOINC), and *SNOMED Clinical Terms* (SNOMED CT).
Methods: The potential of each terminology to encode five exemplary laboratory results is assessed. The terminologies are evaluated according to scope, correctness, formal representations, and ease of use.
Results: NPU is based on metrological concepts with strict rules regarding the coding of the measurand and the result value. Clinically equivalent results are regularly mapped to the same code but there is little support to differentiate results from non-standardized measurements. LOINC encodes analyses as offered by the laboratory. Its large number of entries allows different mappings for the same analysis. SNOMED CT contains few analyses natively, but its formal composition mechanism allows representing measurements by post-coordinated expressions that are equivalent to LOINC codes. SNOMED CT's strength lies in its support of many non-numerical result values. Implicit code hierarchies exist in NPU and LOINC. SNOMED CT has explicit, elaborate axioms that elucidate the meaning of its content. Its complexity and its license conditions, however, impede a more widespread use. Interpretive comments, a crucial part of laboratory results, are still difficult to encode with any of the terminologies.
Conclusions: All three terminologies have distinct potentials and limitations, but the approximation of SNOMED CT and LOINC suggests using them together. Terminologies need to be expanded to also cover interpretive comments.

Keywords: data exchange; information technology; interoperability; LOINC; metrology; NPU; SNOMED CT; terminology; vocabulary.

Introduction

Medical laboratories do not only measure analytes, but also strive to make their results actionable for patient treatment. They ensure that the laboratory reports are correctly transmitted to the requesting physician with a short turnaround time [1]. Laboratories also assist in the interpretation of their results by providing comments [2], statements regarding measurement uncertainty, reference intervals, medical decision limits, or other means. With the ever-increasing portfolio of available laboratory tests, these services will likely gain more importance.

These tasks already require increasing support by information technology. Electronically transmitted laboratory reports reach their recipient faster. Interpretive comments are often added based on complex rules that are evaluated by the laboratory information management system [3, 4].

While these systems fulfil their requirements as long as one laboratory does all measurements, limitations become obvious in complex treatment pathways that involve multiple laboratories. Here, the individual laboratories are often not aware of measurements that they have not performed themselves. Such difficulties in reliably exchanging laboratory results electronically may severely impact the quality of patient care. Interoperability of clinical data – between labs, institutions, and jurisdictions – is not limited to data transmission alone. The desideratum is *semantic* interoperability, i.e. the exchange of meaningful data based on a common semantic reference, such as domain terminologies that provide codes and terms together with definitions [5]. These data standards have the potential to facilitate biomedical research and

***Correspondence: Dr. med. Andreas Bietenbeck,** Institut für Klinische Chemie und Pathobiochemie, Klinikum rechts der Isar TU München, Ismaninger Str. 22, München 81675, Germany, E-Mail: andreas.bietenbeck@tum.de.
http://orcid.org/0000-0002-1228-0770
Martin Boeker: Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany. https://orcid.org/0000-0003-2972-2042
Stefan Schulz: Institute for Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany; Averbis GmbH, Freiburg, Germany; and Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria. https://orcid.org/0000-0001-7222-3287

advance learning in laboratory medicine through meaning-preserving inter-laboratory comparisons [6–8].

In order to evaluate the usefulness of a terminology for laboratory results, the different constituents of a laboratory result have to be recognized (Figure 1). The quantity intended to be measured, also known as measurand [9, 10], resembles a medical question like "how high is the mass concentration of glucose in blood after fasting?". Often, the measurand is supplemented with additional information, e.g. the analytic method (e.g. "mass concentration of glucose in blood after fasting measured with a glucometer"). The outcome of this analysis is a quantitative or qualitative result value (similar to the answer provided by the test). Additionally, interpretive comments enrich the result. Statements regarding measurement uncertainty are mandatory according to some metrological guidelines [11]. They can be seen as a special case of interpretive comments. If a comment exists, it is often of major importance for the correct interpretation.

The scope of a terminology can differ and can encompass only some or all constituents of the information produced by laboratories. A requirement for laboratory terminologies is that they denote laboratory analyses in a concise way. Ideally, clinically equivalent measurements share a common code. Identical analyses may differ only in the way the result is reported, e.g. mass concentration (mg/dL) vs. molar concentration (mmol/L). Equivalent analyses can be merged and displayed synoptically in order to visualize changes and trends. Hypothetically, using terminology-based coding standards, laboratories even can import data from other laboratories and use these results to validate their own new measurements. On the other hand, clinically different results should lead to different codes. The interpreter of laboratory results must be able to differentiate between value changes reflecting a change in the patient and value changes that are merely the result of switching to a different analytical method.

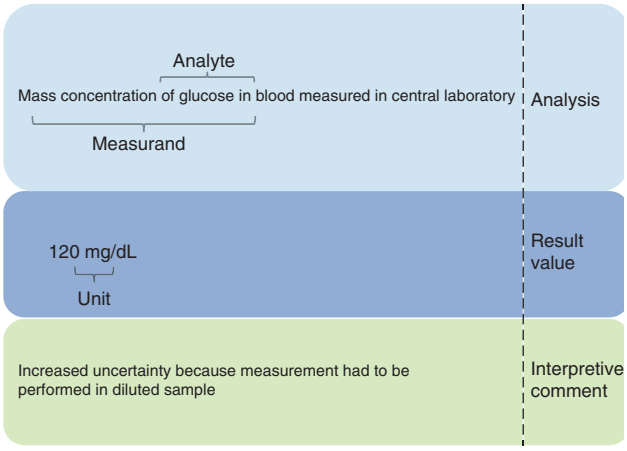

Figure 1: Constituents of a laboratory result using a glucose measurement as an example.

Many scenarios in biomedical research and healthcare need to recognize relationships between different laboratory analyses. For example, Troponin I and Troponin T are clearly distinct analyses, but high levels of both indicate cardiac damage. With a terminology that expresses this information by additional semantic relations, applications such as clinical decision support systems can make better use of laboratory results and enhance patient care.

A drawback of terminologies for laboratory results is that their use is labor-intensive. Good quality coding requires prior training. Even after an initial coding of the analyses, regular updates need to reflect changes in the laboratory or in the terminology. In order to integrate the regular mapping of local terms to terminology codes into the routine of laboratories, the terminology needs to be easy to use and supported by an ecosystem consisting of documentation, user groups, software tools, and other resources.

This work examines how three common terminologies, *Nomenclature for Properties and Units* (NPU), *Logical Observation Identifiers Names and Codes* (LOINC), and *SNOMED Clinical Terms* (SNOMED CT) are able to encode five exemplary laboratory results. The terminologies are then assessed according to four criteria.

Materials and methods

NPU

The NPU is developed by a joint committee of the International Federation of Clinical Chemistry and Laboratory Medicine and the International Union of Pure and Applied Chemistry. Predominantly used in Northern Europe and heavily influenced by metrological concepts, it specifies what property of the patient is measured in a laboratory analysis [12]. This property exists independently of the individual measurement. Therefore, an NPU code remains unchanged even if the measurement technology changes [13].

An NPU code describes an analysis along three axes (Figure 2). The *System* axis represents the biologic sample material that is the subject of the examination (e.g. blood). The *Component* axis describes specific components or processes of the material measured (e.g. glucose). Finally, the *Kind-of-Property* axis is the quantity or the nominal property that is measured (e.g. amount-of-substance concentration) [10].

In the current work, we analyze the NPU vocabulary, which in the version of 2018-07-01 contains 21,663 codes.

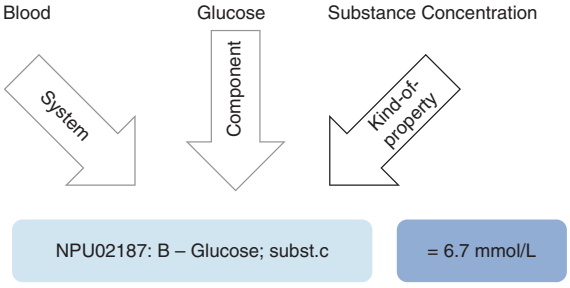

Figure 2: Structure of a *Nomenclature for Properties and Units* (NPU) code using a glucose measurement as an example.

LOINC

LOINC, a terminology standard issued by the Regenstrief Institute (US), assigns codes to laboratory measurements and other medical observations. LOINC codes are defined by six so-called parts (Figure 3) [14]. Three of these LOINC parts resemble NPU axes. The *System* part describes the sample material (e.g. serum). The *Component or Analyte* part provides the name of the measured analyte, together with further special measurement conditions such as a challenge (e.g. blood glucose challenged by an oral glucose tolerance test). The *Property* part specifies the quantity of the analyte that is being measured (e.g. mass or concentration). In addition to the NPU properties, the *Time* part specifies whether the measurement covers a moment in time or a time interval, whereas the *Scale* part specifies the level of measurement such as quantitative, ordinal, or nominal. The optional *Method* part should be used whenever different analytical methods lead to clinically different results. Besides these main parts, LOINC comes with additional information such as the laboratory subspecialty (e.g. hematology) of the code, the commonly used units, or whether the code should be used for a laboratory order (e.g. request for a complete blood count) or for an observation (e.g. hemoglobin).

In the current work, we examine LOINC version 2.64. It contains 79,869 "ACTIVE" codes, thereof 51,813 codes are from the "Laboratory class".

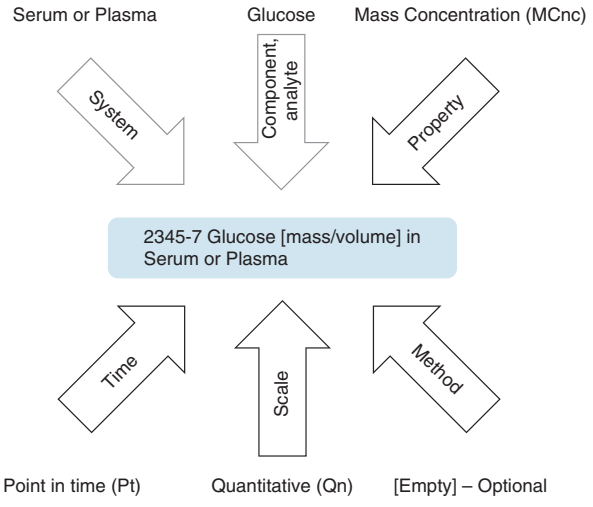

Figure 3: Structure of a *Logical Observation Identifiers Names and Codes* (LOINC) code using a glucose measurement as an example.

SNOMED CT

SNOMED started 50 years ago as a pathology-centerd nomenclature and grew into subsequent versions of a multiaxial nomenclature system covering the whole of clinical medicine. Its version 3 provided 18 axes each of which corresponded to a single hierarchy under a clinical category like *Body structure*, *Clinical finding*, or *Observable entity*. In the recent versions RT and CT, SNOMED was embedded into a description logic framework [15] and promoted as the international terminology standard SNOMED CT by the international non-profit organization SNOMED International. SNOMED CT is now the largest biomedical ontology with about 300,000 concepts, arranged in a multi-hierarchical taxonomic order. It is enriched by multiple describing and defining logical axioms.

The *Observable entity* hierarchy natively contains so-called pre-coordinated concepts for laboratory results (Figure 4). Some codes that relate to laboratory analyses also exist under the *Procedures* hierarchy [e.g. *42525009 | Partial thromboplastin time, activated (procedure)* |], but they have a slightly different meaning. They describe the activities performed and not the information entities that result. Opposed to pre-coordinated concepts, SNOMED CT's axiomatic framework supports the assembling of new concepts, so-called post-coordinated expressions, guided by the SNOMED CT compositional grammar [16].

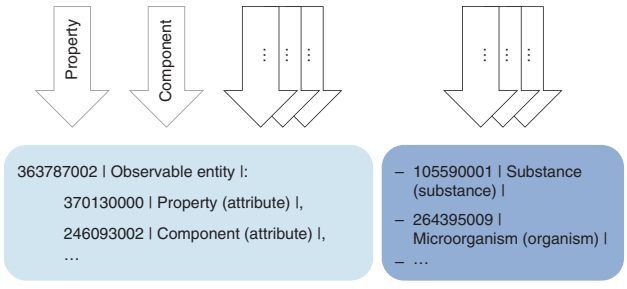

Figure 4: Structure of a *SNOMED Clinical Terms* (SNOMED CT) concept for both analyses and non-numerical result values. All concepts can be further specified with attributes and SNOMED CT's compositional grammar.

In this work, we examine SNOMED CT using its international version 20180131.

Exemplary laboratory results

We test how well the three laboratory terminologies under scrutiny encode the following statements that denote the result of a laboratory measurement:

1. Glucose measured from venous blood with automated analysers in a central laboratory reported as 120 mg/dL.
2. Glucose measured from capillary blood using a plasma-calibrated point-of-care testing (POCT) device reported as 8.9 mmol/L.
3. Anti-cardiolipin IgG antibodies measured in serum by enzyme-linked immunosorbent assay (ELISA) reported as 100 U/mL.
4. Activated partial thromboplastin time in citrated plasma reported as greater than 180 s. An interpretive comment states that these results are most likely caused by (wrong) sampling through a heparin contaminated intravenous line.
5. Cell culture of a cervical smear sample identified very high numbers (+++) of Enterobacter aerogenes. The bacterium is resistant to amoxicillin.

Criteria: The following criteria are used to assess the ability to encode the exemplars:

- Scope: which parts of the laboratory result can be encoded?
- Correctness: clinically equivalent laboratory analyses should be encoded with the same code, and clinically non-equivalent laboratory analyses should be coded with different codes.
- Formal relations: relationships between different analyses should be expressed formally and thus be accessible to automated analyses by information technology.
- Ease of use: the terminology should be easy to use and should be supported by a well-maintained "ecosystem", consisting of tools, websites, community, educational material.

Results

Encoding of exemplary laboratory results

NPU

1. NPU02187: B – Glucose; subst.c. = 6.7 mmol/L
2. NPU10113: B(cB) – Glucose; subst.c. = 8.9 mmol/L
3. NPU28911: P – Cardiolipin antibody (IgG); arb.subst.c. (IRP 67/086; proc.) = 100×10^3 IU/L
4. NPU01682: P – Coagulation, surface-induced; time (proc.) = >180 s
5. NPU06087: Vagf – Bacterium; taxon (proc.) = Enterobacter aerogenes (cell culture)
   - NPU13746: Vagf – Bacterium (Enterobacter aerogenes.); suscept. (list; ord.sc.; R I S)
   - NPU06001 Syst – Amoxicillin; suscept. = R
   - Note: R: Resistant; I: Intermediate; S: Susceptible

Each NPU term starts with a unique identifier, followed by a description and finally the result value. NPU allows reporting blood glucose only as molar concentration but not as mass concentration, because only the former is the unit recommended by the International System of Units. Cardiolipin antibody must be reported as 10^3 IU/L and not, e.g. as IU/mL [12]. In clinical documentation, units of measurement are of great importance and laboratories change them only cautiously to avoid erroneous interpretation [17]. If the traditionally reported unit does not suit the NPU terminology, the laboratory will most likely convert it internally just for NPU coding. Whenever possible, NPU draws on existing metrological standards. The NPU code for cardiolipin IgG antibody explicitly refers to the International Reference Preparation lot 67/86 [18]. When an analysis is calibrated according to a different standard, a different NPU code has to be used. NPU does not offer a way to describe the sample collection error. For a set of codes, the NPU system supports lists as result type. Lists can group analyses – again specified as NPU codes – that are closely related such as susceptibility of a bacterium to different antibiotics [19].

LOINC

1. 2345-7 Glucose [Mass/volume] in Serum or Plasma: 120 mg/dL
2. 14743-9 Glucose [Moles/volume] in Capillary blood by Glucometer: 8.9 mmol/L
3. 3181-5 Cardiolipin IgG Ab [Units/volume] in Serum by Immunoassay: 100 [GPL'U]/mL
4. 14979-9 aPTT in Platelet poor plasma by Coagulation assay: >180 s
5. 11261-5 Bacteria identified in Vaginal fluid by Aerobe culture: Enterobacter aerogenes
   18861-5 Amoxicillin [Susceptibility]: R (Note: R: Resistant; I: Intermediate; S: Susceptible)

Each LOINC term also starts with a unique identifier. LOINC aims to encode a laboratory analysis pragmatically

as it is offered by the laboratory. LOINC does not specify the layout of the result value. Therefore, the non-numerical result value "Enterobacter aerogenes" is not part of the terminology. In addition, the sample collection error cannot be described.

SNOMED CT

1. 434912009 | Blood glucose concentration (observable entity) | - > 120 mg/dL
2. 363787002 | Observable entity |:
   370130000 | Property (attribute) | = 118539007 | Mass concentration (property) (qualifier value) |,
   704327008 | Direct Site | = 122554006 | Capillary blood specimen (specimen) |,
   246093002 | Component | = 67079006 | Glucose (substance) |,
   370132008 | Scale | = 30766002 | Quantitative |,
   370134009 | Time aspect | = 123029007 | Single point in time | - > 8.9 mmol/L
3. 363787002 | Observable entity |:
   370130000 | Property (attribute) | = 118569000 | Arbitrary concentration (property) (qualifier value) |,
   704327008 | Direct Site | = 122555007 | Venous blood specimen (specimen) |,
   246093002 | Component | = 710401005 | Immunoglobulin G antibody to cardiolipin (substance) |,
   72394005 | Technique (qualifier value) | = Enzyme immunoassay technique (qualifier value) |
   370132008 | Scale | = 30766002 | Quantitative |,
   370134009 | Time aspect | = 123029007 | Single point in time | - > 100 [GPL'U]/mL
4. 363787002 | Observable entity |:
   370130000 | Property (attribute) | = 762636008 | Duration (property) (qualifier value) |,
   704327008 | Direct Site | = 122555007 | Venous blood specimen (specimen) |,
   704321009 | Characterizes (attribute) | = 737095005 | Activated clotting process (qualifier value) |,
   370132008 | Scale | = 30766002 | Quantitative |,
   370134009 | Time aspect | = 123029007 | Single point in time | - > > 180 s
   151271000119102 | Abnormal blood test (finding) |:
   363713009 | Has interpretation (attribute) | = 274894003 | Unexplained laboratory result (qualifier value) |
5. 363787002 | Observable entity |:
   370130000 | Property (attribute) | = 118584009 | Presence OR identity (property) (qualifier value) |,
   272394005 | Technique (qualifier value) | = 702658000 | Microbial culture technique (qualifier value) |,
   704327008 | Direct Site | = 276446009 | Cervical smear sample (specimen) |,
   704321009 | Characterizes (attribute) | = 441862004 | Infectious process (qualifier value) |
   117363000 | Ordinal value (qualifier value) |,
   370134009 | Time aspect | = 123029007 | Single point in time | - >
   (62592009 | Enterobacter aerogenes (organism) | + 710877000 | Beta lactam resistant bacteria (organism) |)

SNOMED CT terms are identified by a unique identifier (concept ID). The description concept Reference is enclosed by a pair of "|" characters. The first laboratory result exemplar is coded with a pre-coordinated SNOMED CT concept under the *Observable entity* hierarchy. The other exemplary laboratory results are mapped to post-coordinated concepts, which also inherit from an *Observable entity*. The ":" sign initiates a subexpression for further refinement. The equal sign " = " connects attribute names and their value. The "- > " sign is used here to separate the laboratory observation and the result, but it is not part of SNOMED CT.

For the second laboratory result exemplar, we were unable to specify the test as a point-of-care test. Possible attributes of the observable entity were 246501002 | 424226004 | Using device (attribute) |, but SNOMED CT contains glucometer only as a procedure and not as a device. Another alternative is to specify a 246501002 | Technique (attribute) |, but we also were unable to find an appropriate technique. For the fourth exemplary laboratory result, we added the interpretation of a possible sampling error as "Unexplained laboratory result".

SNOMED CT has the widest scope but no terminology fully supports interpretive comments

Each NPU code specifies both the analysis and the result value including the precise unit. For result values that are non-numerical, e.g. identified bacteria in microbiology results, NPU is less strict and allows, e.g. bacteria names or references to an American Type Culture Collection (ATCC) code value. NPU is not intended to further qualify a measurement or to add a medical interpretation.

LOINC focuses on description of the analysis. A specific structure for result values is not part of the standard. LOINC codes only specify the measured property (e.g. mass concentration) but not the reported unit (e.g. mg/dL).

To this end, the Unified Code for Units of Measure (UCUM) system is recommended to express units together with LOINC codes [20]. LOINC has codes to describe sample quality (e.g. 20393-5 Sample hemolyzed) but lacks a mechanism to encode interpretive comments or measurement uncertainty.

SNOMED CT requires the use of the post-coordination mechanism in order to specify most laboratory analyses from the *Observable entity* hierarchy. For some non-numerical result values, such as microorganisms or substances, SNOMED CT offers specific codes. For some analyses, e.g. from microbiology, the sampling aspect is very important. SNOMED CT offers a greater expressiveness for sampling sides than NPU or LOINC. SNOMED CT offers very basic codes for describing measurement uncertainty or interpretive comments.

NPU regularly ensures the same code for clinically equivalent analyses, LOINC and SNOMED CT are less strict

NPU specifies the property of a system that is measured independently of the means or techniques used, although laboratory medicine usually offers several ways to measure an analyte. Often these methods produce clinically equivalent results. However, if more than one independent analyte definition and reference standard exists concurrently, there is most likely a medical reason for this. By referring to such standards, the concept of NPU ensures that the same code is used regularly for clinically equivalent analyses. However, for many analyses, measuring methods are not sufficiently standardized or harmonized. In these cases, the method used is of great medical importance. NPU lacks the ability to account for the method, which entails that the same code might be used for clinically different analyses.

The coding of blood glucose measurements with a glucometer is an interesting special case. Although the sample material is capillary blood, results are referenced to plasma [21]. Similarly, new wearable sensors measure glucose in interstitial fluids. The displayed results are again mathematically converted to the equivalent glucose concentrations in plasma. Therefore, there are good arguments that in the NPU terminology all these analyses should be coded as glucose concentration in plasma.

LOINC frequently offers multiple ways to encode the same laboratory analysis. For instance, measurements coded as "2345-7 Glucose [Mass/volume] in Serum or Plasma" can also be coded as "74774-1 Glucose [Mass/volume] in Serum, Plasma or Blood". For most LOINC codes with a "Substance Concentration", there is also an equivalent code with a "Mass Concentration". Although mass and substance concentrations can be mathematically converted, LOINC still assigns distinct terms. The number of LOINC terms keeps growing fast due to LOINC's combinatorial design. In order to use LOINC terms from different sources, they might have to be converted to a common set of LOINC terms and units [22]. LOINC's *Method* part can often be used to differentiate between clinically non-equivalent measurements.

For many laboratory analyses, pre-coordinated SNOMED CT concepts do not offer enough granularity. This is not a weakness but a design feature, which follows from the agreement between LOINC and SNOMED International. With the intention to avoid overlap between SNOMED CT and LOINC, this agreement [23] recommends that post-coordinated SNOMED CT expression fill these gaps. The problem that there are sometimes several ways to represent the same laboratory analysis [24] is at least partially solved by the underlying logic, which allows assessing whether concepts are related.

Formal definition of relationships in SNOMED CT allows for better computational analyses

Both NPU and LOINC do not formally specify semantic relationships between codes. As a remedy, LOINC has introduced "Groups" and a "Multiaxial Hierarchy", but both approaches are still work in progress. However, the components that fill the NPU axis and LOINC parts are of different granularity [25, 26]. "Arterial blood" is more specific than "blood". Any NPU or LOINC code that uses "arterial blood" is, by itself, more specific than the same code that uses "blood" instead. Therefore, the different granularities in axis and parts *imply* a hierarchy of the codes, but do not formalize it in mathematical terms. Similar generalizations can be found in other LOINC parts. The naming scheme for the *Component* part separates sub-classifications (e.g. *Calcium.ionized*) from their more unspecific main analysis (e.g. *Calcium*) using suffixes separated by a period [27]. A code that specifies the *Method* part is more specific than a code that does not.

In NPU, 7914 codes contain a specification of the *System* axis (sample material). In LOINC, there are exactly 1000 active codes in the laboratory class that are identical to another code but further specify a blood sample. A total of 6146 codes are a more precise specification of methodless codes and 11,454 codes differ only in the *Property* part.

Among these, 3856 codes use mass or substance concentration and can be mathematically converted into each other.

However, with their unclear semantic, these only informally specified hierarchies can lead to problematic interpretations. For some analyses, it is unclear whether the analyses themselves are unspecific or whether a generic code subsumes analyses with different specifications. For example, many analyses detect antibodies regardless of their subclass. A code that uses an "antibody" *Component* part (without a subclass) can exactly identify their result. An examination of these results over time might indicate a change in the patient. The same code could also be used to aggregate different tests that specifically measure IgG, IgE, and IgM antibodies. Changes in these results can be caused by a real change in the patient or by a different analytical assay. Moreover, logical inferences might also be problematic if relationships are not carefully modeled [28].

Relationships between concepts are formally defined in SNOMED CT. For example, the concept "122554006 | Capillary blood specimen (specimen) |" is related via the subclass relation "Is a" to the concept "119297000 | Blood specimen (specimen) |". Any search for a "363787002 | Observable entity |" with "119297000 | Blood specimen (specimen) |" as "704327008 | Direct Site |" will also return concepts specified with "122554006 | Capillary blood specimen (specimen) |".

All vocabularies are supported by a well-developed ecosystem, but the usage of LOINC seems to be the easiest one

Development of the NPU terminology is overseen by a Steering Committee that includes IFCC representatives. Updates are published monthly. The website http://www.npu-terminology.org provides information and a searchable database for NPU terms. Much of the documentation is spread over several scientific publications. The terminology can be used free of charge. An English and a Danish version exist but no German translation is available. Coding a laboratory analysis with NPU requires some understanding of laboratory medicine, but the simple structure of the terminology is easy to comprehend.

Regenstrief releases updates for LOINC twice a year. It also releases a program called Regenstrief LOINC Mapping Assistant to facilitate mapping and operates http://www.loinc.org with extensive information. Other LOINC mapping tools that can automatically map over 70% of the analyses have been created by the scientific community [29, 30]. LOINC has been translated into several languages. For German, an Austrian, a Swiss, and a version produced by the German "Deutsches Institut für Medizinische Dokumentation und Information (DIMDI)" are available. In the Austrian personal health record platform "elektronische Gesundheitsakte" known as ELGA (personalised electronic health record), LOINC is the terminology used for storing and exchanging laboratory data [31]. Usage is free of charge. Because of this well-developed ecosystem and the simple concept of LOINC, it is easy to learn [32].

SNOMED CT is managed by an international standards development organization, called SNOMED International (former IHTSDO). Its usage depends on corporate, research, or national licences. There are still some European countries without a national license (e.g. France, Germany, Austria, Italy), although SNOMED CT has been recommended by the European Commission as appropriate for eHealth interoperability within Europe [33].

Extensive documentation of SNOMED CT is freely available on the website (https://www.snomed.org/snomed-ct). Mapping and browsing tools are made available by SNOMED Intl. (e.g. http://browser.ihtsdotools.org) and by other organizations. Translations are available for some languages but not for German. Because of the great complexity of SNOMED CT and the broad range of covered domains, mapping with SNOMED CT requires extensive medical and methodological knowledge [34–36].

Discussion

In this work, we have demonstrated how five exemplary laboratory results could be successfully encoded using each of the three terminologies NPU, LOINC, and SNOMED CT. NPU's strength lies in its sound foundation in metrology. LOINC has a more pragmatic approach and a large number of codes. Mapping is relatively easy. SNOMED CT relates its concepts by logic-based axioms and allows specifying some information such as non-numeric result values, a feature that is not present in LOINC and NPU.

However, no terminology completely fulfils all requirements of an easy-to-use, interoperable system. That NPU cannot differentiate between clinically non-equivalent measurements is deeply rooted in its design and cannot be changed easily. LOINC offers a greater granularity but different codes can be assigned to the same laboratory test. Its implicit hierarchies can help combine medical equivalent analyses. In contrast to NPU and LOINC, the routine use of SNOMED CT requires a license. Its complex post-coordination mechanism entails more difficulty than the other terminologies, but it should not be neglected that

when using SNOMED CT all aspects of clinical documentation are represented by a single terminology standard.

Besides NPU, LOINC, and SNOMED CT, other vocabularies exist to code laboratory results. In Germany, "LDT 3" (LDT = Labordatentransfer) data transfer standard is used for communication of laboratory data in the outpatient sector but has no international significance. For some specialties, dedicated nomenclatures exist such as the Human Genome Organisation (HUGO) Gene Nomenclature, a terminology already linked to both LOINC and SNOMED CT [33]. As mentioned, Regenstrief Institute and SNOMED International have started a formal cooperation on LOINC – SNOMED CT harmonization. This draws a clear line between the two terminologies: SNOMED CT will provide the conceptual content as well as the compositional semantics for LOINC, and LOINC codes can then be seen as equivalent to post-coordinated SNOMED CT expressions.

It is important to realize that NPU, LOINC, and SNOMED CT only encode the results of single laboratory analyses. However, the complete result of a clinical laboratory order is a laboratory report. To represent these reports, several information models exist. Fast Healthcare Interoperability Resources, the newest iteration of the HL7 family of healthcare data transfer protocols, contains the "DiagnosticReport" and "Observation" resources to transmit reports [37]. LOINC and SNOMED CT terms are preferred elements of this standard. The HL7 clinical document architecture (CDA) can also encode a laboratory report electronically with the LOINC and the SNOMED CT terminology [38]. In short, these documents (e.g. a special pdf file) contain information in the form of human-readable text with a layout together with the same information in a structured, machine-readable way.

Unfortunately, interpretive comments have not been standardized so far. None of the three terminologies under scrutiny offers more than rudimentary support of interpretive comments. Therefore, interpretive comments are difficult to be interoperably transferred, on the level of the report as little as on the level of a single analytical result. In order to increase patient safety, these gaps should be urgently filled, especially for those comments that concern measurement uncertainty.

Terminologies do not intend to harmonize or standardize measurements. If a measurement is not comparable across laboratories, this problem is likely to arise both in clinical practice and in electronic data transfer. Laboratory medicine needs to increase its efforts to create comparable results based on reference methods and reference materials [39]. Often different results arise from different assay manufactures. Unfortunately, existing terminologies are not granular enough to separate these results [40]. The Global Unique Device Identification Database (https://accessgudid.nlm.nih.gov/) by the US Food and Drug Administration might offer unique identifiers of assays that can extend existing terminologies.

Our scrutiny of the three terminology standards has shown potentials and limitations in each of them, in terms of coverage, semantic precision, and free access. The approximation of SNOMED CT and LOINC suggests using them together, at least in the jurisdictions where SNOMED CT can be freely used. Because interpretive comments especially concerning measurement uncertainty are a crucial part of a laboratory result, terminologies need to be expanded to cover this information.

Acknowledgments: The authors would like to thank Romina Rösch for her helpful comments.
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Hawkins RC. Laboratory turnaround time. Clin Biochem Rev 2007;28:179–94.
2. Vasikaran S, Sikaris K, Kilpatrick E, French J, Badrick T, Osypiw J, et al. Assuring the quality of interpretative comments in clinical chemistry. Clin Chem Lab Med 2016;54:1901–11.
3. Rhoads DD, Sintchenko V, Rauch CA, Pantanowitz L. Clinical microbiology informatics. Clin Microbiol Rev 2014;27:1025–47.
4. Baron JM, Dighe AS. The role of informatics and decision support in utilization management. Clin Chim Acta 2014;427:196–201.
5. Park H-A, Hardiker N. Clinical terminologies: a solution for semantic interoperability. J Korean Soc Med Inform 2009;15:1–11.
6. Bietenbeck A, Fabian P. Learning health systems and laboratory medicine. Stud Health Technol Inform 2018;253:104–8.
7. Detmer DE. Building the national health information infrastructure for personal health, health care services, public health, and research. BMC Med Inform Decis Mak 2003;3:1.
8. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016;3:160018.
9. De Bièvre P. "Analyte" is frequently used as synonym for "measurand": is that correct? Accredit Qual Assur 2013;18:71–2.
10. BIPM I, IFCC I, IUPAC I, ISO O. The international vocabulary of metrology – basic and general concepts and associated terms

(VIM), 3rd ed. JCGM 200: 2012. JCGM (Joint Committee for Guides in Metrology). 2012.
11. White GH, Farrance I, Group AUoMW. Uncertainty of measurement in quantitative medical testing: a laboratory implementation guide. Clin Biochem Rev 2004;25:S1–24.
12. Petersen UM, Dybkær R, Olesen H. Properties and units in the clinical laboratory sciences. Part XXIII. The NPU terminology, principles, and implementation: a user's guide (IUPAC Technical Report). Pure Appl Chem 2011;84:137–65.
13. Joint Committee on Nomenclature P, Units of the I, Iupac, Pontet F, Petersen UM, Fuentes-Arderiu X, et al. Clinical laboratory sciences data transmission: the NPU coding system. StudHealth Technol Inform 2009;150:265–9.
14. McDonald CJ, Huff SM, Suico JG, Hill G, Leavelle D, Aller R, et al. LOINC, a universal standard for identifying laboratory observations: a 5-year update. Clin Chem 2003;49:624–33.
15. Baader F, Calvanese D, McGuinness DL, Nardi D, Patel-Schneider PF. The description logic handbook: theory, implementation and applications. New York, NY: Cambridge University Press, 2010:624.
16. SNOMED C. Compositional Grammar Specification and Guide v2. 02. IHTSDO (22 May 2015). 2017.
17. Kilpatrick ES, Rigby AS, Atkin SL, Barth JH. Glycemic control in the 12 months following a change to SI hemoglobin A1c reporting units. Clin Chem 2013;59:1457–60.
18. Baudner S. Why a new international reference preparation (IRP) for human plasma proteins? J Clin Lab Anal 1993;7:273–7.
19. Forsum U, Olesen H, Frederiksen W, Persson B. Properties and units in the clinical laboratory sciences. Part VIII. Properties and units in clinical microbiology (Technical Report) (IFCC-IUPAC 1999). Pure Appl Chem 2000;72:555–745.
20. Schadow G, McDonald CJ. The unified code for units of measure (UCUM). Regenstrief Institute and Indiana University School of Informatics. 2017(2.1). Available online at: http://unitsofmeasure.org/ucum.html
21. D'Orazio P, Burnett RW, Fogh-Andersen N, Jacobs E, Kuwa K, Kulpmann WR, et al. Approved IFCC recommendation on reporting results for blood glucose (abbreviated). Clin Chem 2005;51:1573–6.
22. Hauser RG, Quine DB, Ryder A, Campbell S. Unit conversions between LOINC codes. J Am Med Inform Assoc 2018;25:192–6.
23. New Regenstrief and IHTSDO agreement to make EMRs more effective at improving health care [press release]. 2013. Available online at: https://loinc.org/news/new-regenstrief-and-ihtsdo-agreement-to-make-emrs-more-effective-at-improving-health-care/
24. Chiang MF, Hwang JC, Yu AC, Casper DS, Cimino JJ, Starren J. Reliability of SNOMED-CT coding by three physicians using two terminology browsers. AMIA Annu Symp Proc 2006;2006:131–5.
25. Eilbeck K, Jacobs J, McGarvey SR, Vinion C, Staes CJ, editors. Exploring the use of ontologies and automated reasoning to manage selection of reportable condition lab tests from LOINC. 4th International Conference on Biomedical Ontology; 2013; Montreal; Canada.
26. Steindel S, Loonsk JW, Sim A, Doyle TJ, Chapman RS, Groseclose SL. Introduction of a hierarchy to LOINC to facilitate public health reporting. In Proceedings of the AMIA Symposium 2002. American Medical Informatics Association, San Antonio, TX, USA, 737.
27. McDonald C, Huff S, Deckard J, Armson S, Abhyankar S, Vreeman DJ. Logical Observation Identifiers Names and Codes (LOINC®) users' guide. Loinc_2.64_UsersGuide_2.64 ed: REGENSTRIEF INSTITUTE, INC; 2018.
28. Mary M, Soualmia LF, Gansel X, Darmoni S, Karlsson D, Schulz S, editors. Ontological Representation of Laboratory Test Observables: challenges and perspectives in the SNOMED CT observable entity model adoption. Cham: Springer International Publishing, 2017.
29. Lee LH, Gross A, Hartung M, Liou DM, Rahm E. A multi-part matching strategy for mapping LOINC with laboratory terminologies. J Am Med Inform Assoc 2014;21:792–800.
30. Zunner C, Burkle T, Prokosch HU, Ganslandt T. Mapping local laboratory interface terms to LOINC at a German university hospital using RELMA V.5: a semi-automated approach. J Am Med Inform Assoc 2013;20:293–7.
31. Seerainer C, Sabutsch SW. eHealth terminology management in Austria. Stud Health Technol Inform 2016;228:426–30.
32. Lin MC, Vreeman DJ, McDonald CJ, Huff SM. Correctness of voluntary loinc mapping for laboratory tests in three large institutions. AMIA Annu Symp Proc 2010;2010:447–51.
33. Campbell WS, Karlsson D, Vreeman DJ, Lazenby AJ, Talmon GA, Campbell JR. A computable pathology report for precision medicine: extending an observables ontology unifying SNOMED-CT and LOINC. J Am Med Inform Assoc 2017;25:259–66.
34. Kim SY, Kim HH, Shin KH, Kim HS, Lee JI, Choi BK. Comparison of knowledge levels required for SNOMED-CT coding of diagnosis and operation names in clinical records. Healthc Inform Res 2012;18:186–90.
35. Lee D, Cornet R, Lau F, de Keizer N. A survey of SNOMED-CT implementations. J Biomed Inform 2013;46:87–96.
36. Min H, Zheng L, Perl Y, Halper M, De Coronado S, Ochs C. Relating complexity and error rates of ontology concepts. More complex ncit concepts have more errors. Methods Inf Med 2017;56:200–8.
37. Andersen MV, Kristensen IH, Larsen MM, Pedersen CH, Goeg KR, Pape-Haugaard LB. Feasibility of representing a danish microbiology model using FHIR. Stud Health Technol Inform 2017;235:13–7.
38. Muller ML, Uckert F, Burkle T, Prokosch HU. Cross-institutional data exchange using the clinical document architecture (CDA). Int J Med Inform 2005;74:245–56.
39. Greg Miller W, Myers GL, Lou Gantzer M, Kahn SE, Schonbrunner ER, Thienpont LM, et al. Roadmap for harmonization of clinical laboratory measurement procedures. Clin Chem 2011;57:1108–17.
40. Jones G, Barker A. Standardisation of reference intervals: an Australasian view. Clin Biochem Rev 2007;28:169–73.