Bridging Clinical and Genomic Knowledge: An Extension of the SPHN RDF Schema for Seamless Integration and FAIRification of Omics Data

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Abstract

The Swiss Personalized Health Network (SPHN) is a Swiss research infrastructure initiative that aims to facilitate the exchange of health-related data in a FAIR manner. The SPHN Dataset and SPHN RDF Schema form an essential part of the SPHN Semantic Interoperability Framework, which currently covers mostly clinical routine data. To facilitate the integration of omics data produced by the SPHN National Data Streams, a genomics extension was developed. This was done in close collaboration with clinicians, researchers, bioinformaticians, and data managers, from Swiss university hospitals, academic research groups and the omics platforms. Here, we present the genomics extension of the SPHN RDF Schema, which can be used to semantically describe genomics experiments and covers both clinical and research domains. The schema centers around the general omics process flow, with concepts that denote the individual steps, such as sample processing, assay, and data processing. Genomics-specific specializations are provided, such as library preparation, sequencing assay, and sequencing analysis. The schema also facilitates in capturing other important omics metadata, such as information about the sequencing instrument, standard operating procedure, and quality control metrics. The extension aligns with existing semantic data models and reuses common biomedical vocabularies, such as EDAM, OBI and FAIR genomes, as value sets, thereby facilitating semantic interoperability. It will be used to FAIRify data that is produced within the Swiss network and to facilitate sharing this data as one knowledge graph for reuse among its participants.

Keywords

Genomics, FAIR, SPHN, RDF, NGS, clinical, data model, Semantic web

1. Introduction

The Swiss Personalized Health Network (SPHN) [1] is a research infrastructure initiative focused on establishing an enabling framework to support the sharing of health-related data in accordance with the FAIR principles [2]. At the heart of this initiative is the SPHN Semantic Interoperability Framework, a comprehensive system that provides semantic artifacts for the representation, validation, and statistical analysis of health data. Additionally, a tool stack is in place to support researchers and hospitals in effectively utilizing this technology. Built on the Semantic Web stack, the framework leverages Resource Description Framework (RDF), Web Ontology Language (OWL), Shape Constraints Language (SHACL), and SPARQL Protocol and RDF Query Language (SPARQL) for its formalization. This foundation ensures a seamless and standardized approach to handling health-related information.

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The 2023.2 release of the SPHN RDF Schema facilitates the semantic representation of clinical data such as diagnoses, routine clinical measurements, and standard lab tests [3] and already provided partial coverage for clinical omics data tailored to a restricted set of specific use-cases. For instance, genomic information is addressed through overarching concepts designed for representing basic genomic variations, including single nucleotide polymorphisms (SNPs). Additionally, it incorporates simple concepts for representing a chromosome, genes, transcripts, and proteins. However, these existing concepts only cover a fraction of the vast genomic, and more broadly the omics landscape. To comprehensively address the diverse needs of SPHN National Data Streams (NDS) [4], particularly in domains such as oncology, pediatric care, and infectious diseases, there is a necessity to expand the SPHN RDF Schema. This expansion will be a key focus in the upcoming 2024.1 release (which will be released in Jan 2024), ensuring that the SPHN RDF Schema aligns with the evolving demands in this critical area.

Here, we present a genomics concept model that covers all aspects of the (clinical) NGS workflow and metadata. This model builds upon the existing SPHN RDF Schema and follows a generalized design to allow for extension to other omics fields. It aligns with existing ontologies and vocabularies, and mirrors the design of common domain data models where applicable.

2. Related work

Data models for capturing (gen)omics data, for instance those of nucleotide repositories such as European Nucleotide Archive (ENA) [5], European Genome-Phenome Archive (EGA) [6] and Genomic Data Commons [7], are already well known, but have their own drawbacks. They are either simple catch-all data models with little semantics, too application-centric, or more focused on study and attribution metadata. Ontologies such as the Ontology for Biomedical investigations (OBI) [8] and Semanticscience Integrated Ontology (SIO) [9] offer high expressivity and ontological rigor. However, they leave room for different ways of representing information and require a solid ontology engineering background. FAIR Genomes [10] broadly fits our use case, but it is too specific for genomics, tailored more towards the data capture side than the optimal data structure, and designed to fit a broad range of data capture applications thereby staying generic. Other approaches are contrasted in section 5. Discussion.

3. Methods

First, a workshop was organized to capture the needs and requirements of stakeholders and map the (gen)omics data domain. Participants from 12 institutions including clinicians, researchers, bioinformaticians, data managers, and leadership, from Swiss university hospitals, technology institutes, and the genome center, collaboratively identified the most relevant concepts, relations, and attributes, as well as the process flow for omics experiments with a focus on genomics. This served as input for follow-up interviews with each NDS, where stakeholders clarified their use cases and domain, and presented example data for each use case. All acquired information about the data domain and (gen)omics workflows was compiled into a 'statements document', *i.e.* a document that lists what was assumed to be true about the domain as simple statements, organized per topic. Stakeholders iteratively provided refinements until consensus was reached.

A review was performed of common (gen)omics data models from nucleotide repositories and platforms, as well as biomedical ontologies and vocabularies, to evaluate whether these could be (partly) reused for intended use cases, requirements, and data.

The final model was validated at a second workshop where participants scrutinized it by applying it to example data of their use cases.

The concept set was formalized using the SPHN Dataset template [11]; SPHN Schema Forge [12] was used to validate the resulting dataset, as well as to generate the corresponding RDF Schema, SHACL validation rules, and SPARQL queries [7].

4. Results

From literature research and the initial workflow that was created in the first workshop, it became clear that omics research could be modeled as a series of consecutive steps, where the output of one step may serve as the input of another. For example, a sample or data may be input for sample or data processing steps. In Figure 1, the order of individual steps is indicated by relating steps that directly precede each other with a 'predecessor' relation, forming a chain or sequence of steps. The material or data that is produced and subsequently produced between preceding steps is indicated using an output or input relation, respectively, but is optional, since this information is not always available or relevant (it is implied). This pattern forms the backbone of the model.

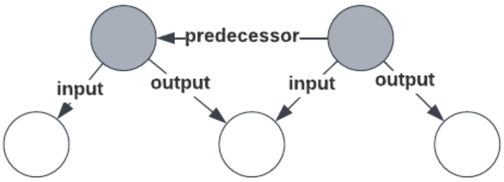


Figure 1: Basic design pattern for expressing steps (in gray) in the omics data flow, where steps that directly precede each other are linked with the 'predecessor' relation, with optional output and input products.

Each step in the omics workflow is a process concept that is composed of essential metadata concepts about that process. The three top-level concepts for representing the omics workflow are 'Sample Processing', 'Assay', and 'Data Processing'. Here, the name 'Assay' was favored over 'Experiment' since the latter has ambiguous interpretation, and is used differently in several data models in the same domain. The 'Sample Processing' concept is composed of zero or more input and/or output 'Sample' concepts, while the 'Data Processing' concept is composed of zero or more input and/or output 'Data File' concepts. The 'Assay' concept is composed of zero or more input 'Sample' concepts and zero or more output 'Data File' concepts. Note that both top level concepts 'Sample Processing' and 'Data Processing' and their descendants may be repeated to express a sequence of processing steps. The documents describing these concepts are available at the SPHN Interoperability Framework Gitlab repository [13].

For the genomics field, special concepts are introduced that derive from these generic concepts: 'Library Preparation' derives from 'Sample Processing', 'Sequencing Assay' from 'Assay', and 'Sequencing Analysis' from 'Data Processing'. Derived concepts inherit every 'composedOf' from their more generic counterpart, and may be consecutively repeated in a similar manner. This portion of the SPHN schema is illustrated in Figure 2 and described in the paragraphs below.

Central to the genomics workflow is the sequencing assay. The 'Sequencing Assay' concept is composed of essential metadata concepts, representing the sequencer ('Sequencing Instrument'), library preparation ('Library Preparation'), intended read length and depth, and zero or more runs ('Sequencing Run'). The 'Sequencing Run' concept represents the actual execution of the assay, and holds information that may vary per run, such as read count, average insert size, average read length, and optional quality control metrics (represented via the 'Quality Control Metric' concept).

The 'Library Preparation' concept is a special type of 'Sample Processing' that is part of a 'Sequencing Assay'. It holds information on the library preparation kit, target enrichment kit, and intended insert size, and, in case a gene panel kit is used as target enrichment, information on the gene panel's focus genes. Any other processing steps that precede an assay's library preparation may be registered using the 'Sample Processing' concept.

Following the sequencing assay, there are one or more data processing steps that manipulate the output of the assay. These are represented by the 'Sequencing Analysis' concept, a specialization of 'Data Processing', that is composed of an optional reference genome.

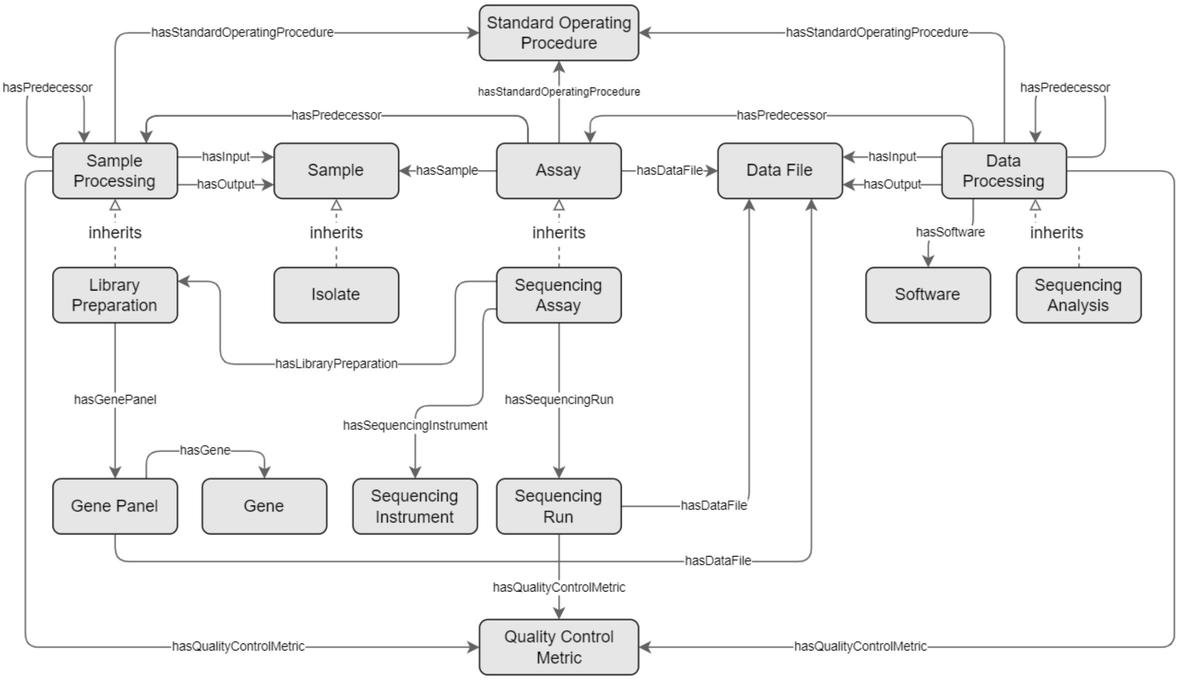


Figure 2: Basic excerpt of the schema for the (gen)omics process flow.

The model further provides utility concepts with general applicability. For instance, 'Standard Operating Procedure' concept was created to provide information about the prescribed step-by-step procedure that was followed to conduct experimental procedures such as sample processing, assays, and data processing. In addition, the 'Quality Control Metric' concept holds information about the value of certain quality control metrics that are relevant for these processes, such as the 'Phred quality score' for DNA sequencing.

The 'Isolate' concept is a specialization of the 'Sample', with a property to indicate the isolated organism, which is relevant for pathogen surveillance research.

Where applicable, concepts are aligned to terms and classes from common public domain terminologies, such as SNOMED CT and OBI, thereby facilitating semantic interoperability. For instance, the 'Assay' concept has a meaning binding to OBI's 'assay' class (OBI:0000070), while 'Isolate' has a meaning binding to SNOMED CT's 'Microbial isolate specimen (specimen)' concept (SNOMED:119303007). In addition, selected subsets or branches from common public terminologies are imposed as value sets for most nominal attributes. For instance, the type of sequence analysis is indicated by descendants of EDAM's [14] 'Analysis' operation, or similar.

The diagram in Figure 3 visualizes an example instance of a sequencing assay and related metadata. Listing 1 gives an RDF representation of the same example; the full RDF in Turtle syntax is available at [15]. Note that, as with other procedure concepts, many of the composite concepts are optional and may be omitted in case this data is not known or not relevant. For instance, a 'Standard Operating Procedure' may not be known or shared, or may be trivial (*i.e.* the operating instructions by the vendor of a platform). Note that each run produces its own data file(s), which may be selected or discarded as input for data analysis, based on quality metrics of the run.

The genomics extension, including corresponding SPHN RDF Schema, SHACL shapes, and SPARQL queries, is distributed as part of the 2024.1 release, and is available for download at the SPHN Interoperability Framework Gitlab repository [13].

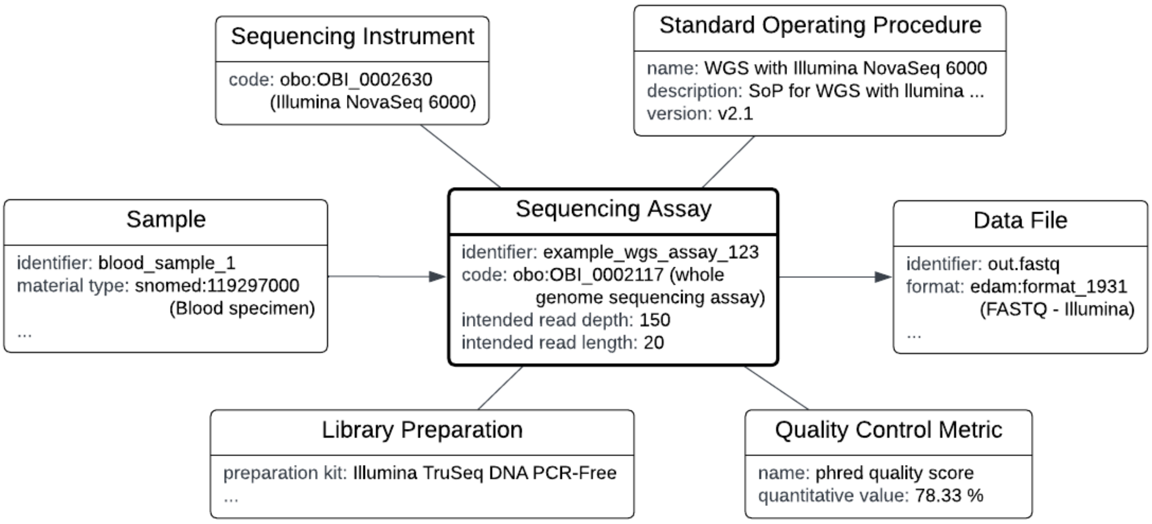
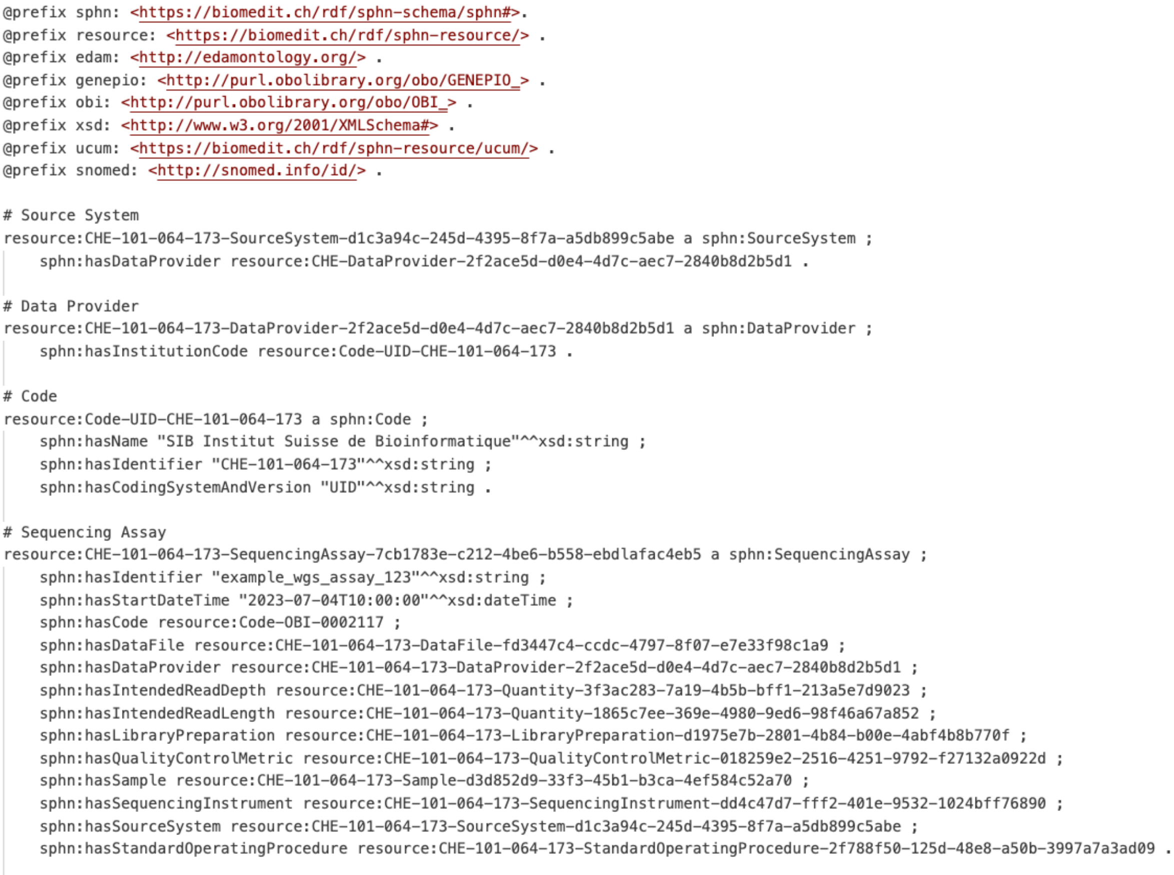

Sequencing Instrument
code: obo:OBI_0002630 (Illumina NovaSeq 6000)
Standard Operating Procedure
name: WGS with Illumina NovaSeq 6000
description: SoP for WGS with llumina ...
version: v2.1
Sample
identifier: blood_sample_1
material type: snomed:119297000 (Blood specimen)
...
Sequencing Assay
identifier: example_wgs_assay_123
code: obo:OBI_0002117 (whole genome sequencing assay)
intended read depth: 150
intended read length: 20
Data File
identifier: out.fastq
format: edam:format_1931 (FASTQ - Illumina)
...
Library Preparation
preparation kit: Illumina TruSeq DNA PCR-Free
...
Quality Control Metric
name: phred quality score
quantitative value: 78.33 %

Figure 3: Diagram visualizing an instance of a sequencing assay that analyzes one sample and produces one FASTQ file. 'Sequencing Assay' concept, together with its 'Instrument', 'Library Preparation', 'Standard Operating Procedure', and 'Quality Control Metric' concepts from which it is composed.

Listing 1: Example instantiation in RDF of a whole genome sequencing assay and related metadata.



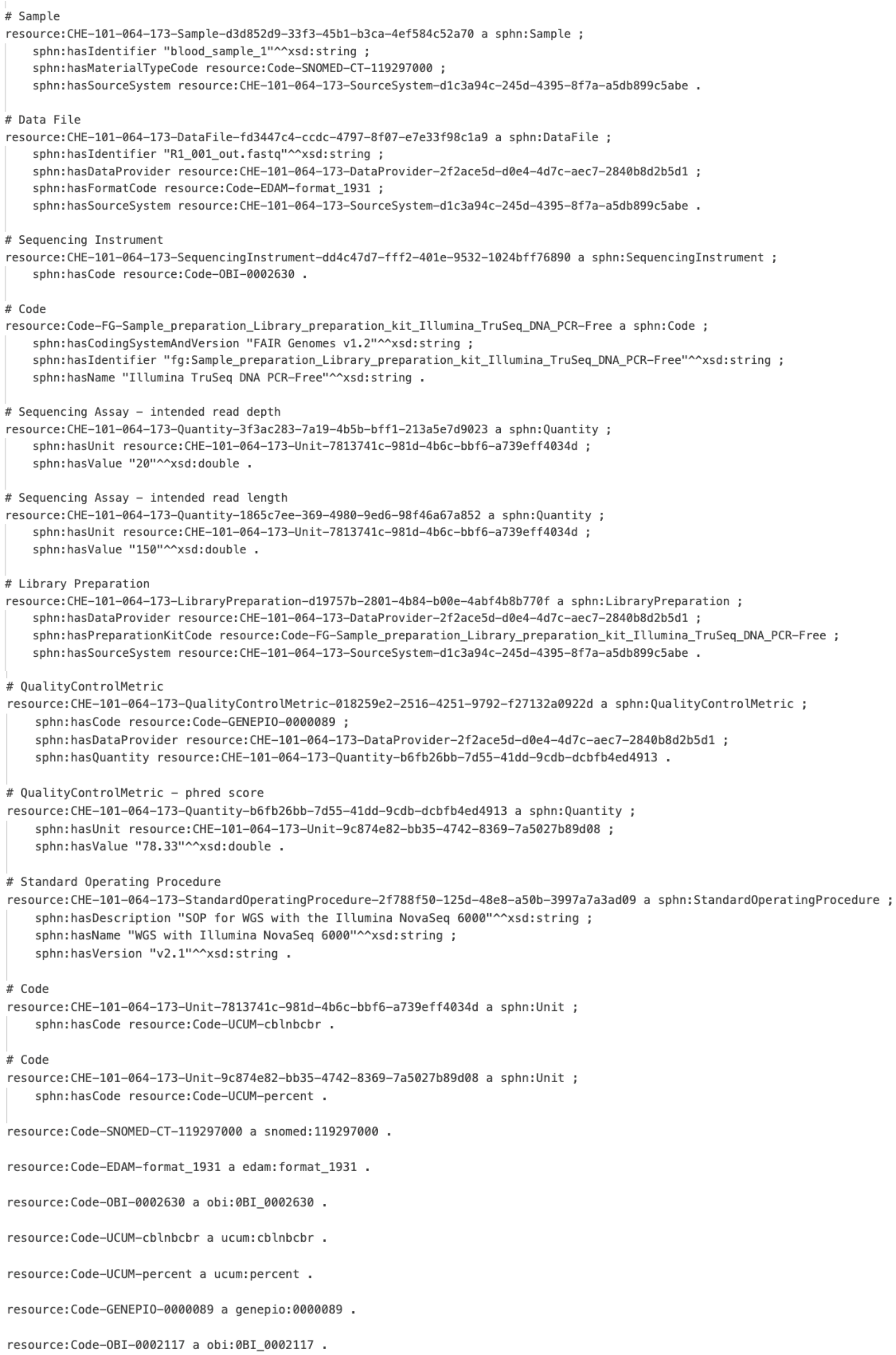
```
@prefix sphn: <https://biomedit.ch/rdf/sphn-schema/sphn#>.
@prefix resource: <https://biomedit.ch/rdf/sphn-resource/> .
@prefix edam: <http://edamontology.org/> .
@prefix genepio: <http://purl.obolibrary.org/obo/GENEPIO_> .
@prefix obi: <http://purl.obolibrary.org/obo/OBI_> .
@prefix xsd: <http://www.w3.org/2001/XMLSchema#> .
@prefix ucum: <https://biomedit.ch/rdf/sphn-resource/ucum/> .
@prefix snomed: <http://snomed.info/id/> .

# Source System
resource:CHE-101-064-173-SourceSystem-d1c3a94c-245d-4395-8f7a-a5db899c5abe a sphn:SourceSystem ;
    sphn:hasDataProvider resource:CHE-DataProvider-2f2ace5d-d0e4-4d7c-aec7-2840b8d2b5d1 .

# Data Provider
resource:CHE-101-064-173-DataProvider-2f2ace5d-d0e4-4d7c-aec7-2840b8d2b5d1 a sphn:DataProvider ;
    sphn:hasInstitutionCode resource:Code-UID-CHE-101-064-173 .

# Code
resource:Code-UID-CHE-101-064-173 a sphn:Code ;
    sphn:hasName "SIB Institut Suisse de Bioinformatique"^^xsd:string ;
    sphn:hasIdentifier "CHE-101-064-173"^^xsd:string ;
    sphn:hasCodingSystemAndVersion "UID"^^xsd:string .

# Sequencing Assay
resource:CHE-101-064-173-SequencingAssay-7cb1783e-c212-4be6-b558-ebdlafac4eb5 a sphn:SequencingAssay ;
    sphn:hasIdentifier "example_wgs_assay_123"^^xsd:string ;
    sphn:hasStartDateTime "2023-07-04T10:00:00"^^xsd:dateTime ;
    sphn:hasCode resource:Code-OBI-0002117 ;
    sphn:hasDataFile resource:CHE-101-064-173-DataFile-fd3447c4-ccdc-4797-8f07-e7e33f98c1a9 ;
    sphn:hasDataProvider resource:CHE-101-064-173-DataProvider-2f2ace5d-d0e4-4d7c-aec7-2840b8d2b5d1 ;
    sphn:hasIntendedReadDepth resource:CHE-101-064-173-Quantity-3f3ac283-7a19-4b5b-bff1-213a5e7d9023 ;
    sphn:hasIntendedReadLength resource:CHE-101-064-173-Quantity-1865c7ee-369e-4980-9ed6-98f46a67a852 ;
    sphn:hasLibraryPreparation resource:CHE-101-064-173-LibraryPreparation-d1975e7b-2801-4b84-b00e-4abf4b8b770f ;
    sphn:hasQualityControlMetric resource:CHE-101-064-173-QualityControlMetric-018259e2-2516-4251-9792-f27132a0922d ;
    sphn:hasSample resource:CHE-101-064-173-Sample-d3d852d9-33f3-45b1-b3ca-4ef584c52a70 ;
    sphn:hasSequencingInstrument resource:CHE-101-064-173-SequencingInstrument-dd4c47d7-fff2-401e-9532-1024bff76890 ;
    sphn:hasSourceSystem resource:CHE-101-064-173-SourceSystem-d1c3a94c-245d-4395-8f7a-a5db899c5abe ;
    sphn:hasStandardOperatingProcedure resource:CHE-101-064-173-StandardOperatingProcedure-2f788f50-125d-48e8-a50b-3997a7a3ad09 .
```



```
# Sample
resource:CHE-101-064-173-Sample-d3d852d9-33f3-45b1-b3ca-4ef584c52a70 a sphn:Sample ;
    sphn:hasIdentifier "blood_sample_1"^^xsd:string ;
    sphn:hasMaterialTypeCode resource:Code-SNOMED-CT-119297000 ;
    sphn:hasSourceSystem resource:CHE-101-064-173-SourceSystem-d1c3a94c-245d-4395-8f7a-a5db899c5abe .

# Data File
resource:CHE-101-064-173-DataFile-fd3447c4-ccdc-4797-8f07-e7e33f98c1a9 a sphn:DataFile ;
    sphn:hasIdentifier "R1_001_out.fastq"^^xsd:string ;
    sphn:hasDataProvider resource:CHE-101-064-173-DataProvider-2f2ace5d-d0e4-4d7c-aec7-2840b8d2b5d1 ;
    sphn:hasFormatCode resource:Code-EDAM-format_1931 ;
    sphn:hasSourceSystem resource:CHE-101-064-173-SourceSystem-d1c3a94c-245d-4395-8f7a-a5db899c5abe .

# Sequencing Instrument
resource:CHE-101-064-173-SequencingInstrument-dd4c47d7-fff2-401e-9532-1024bff76890 a sphn:SequencingInstrument ;
    sphn:hasCode resource:Code-OBI-0002630 .

# Code
resource:Code-FG-Sample_preparation_Library_preparation_kit_Illumina_TruSeq_DNA_PCR-Free a sphn:Code ;
    sphn:hasCodingSystemAndVersion "FAIR Genomes v1.2"^^xsd:string ;
    sphn:hasIdentifier "fg:Sample_preparation_Library_preparation_kit_Illumina_TruSeq_DNA_PCR-Free"^^xsd:string ;
    sphn:hasName "Illumina TruSeq DNA PCR-Free"^^xsd:string .

# Sequencing Assay - intended read depth
resource:CHE-101-064-173-Quantity-3f3ac283-7a19-4b5b-bff1-213a5e7d9023 a sphn:Quantity ;
    sphn:hasUnit resource:CHE-101-064-173-Unit-7813741c-981d-4b6c-bbf6-a739eff4034d ;
    sphn:hasValue "20"^^xsd:double .

# Sequencing Assay - intended read length
resource:CHE-101-064-173-Quantity-1865c7ee-369-4980-9ed6-98f46a67a852 a sphn:Quantity ;
    sphn:hasUnit resource:CHE-101-064-173-Unit-7813741c-981d-4b6c-bbf6-a739eff4034d ;
    sphn:hasValue "150"^^xsd:double .

# Library Preparation
resource:CHE-101-064-173-LibraryPreparation-d19757b-2801-4b84-b00e-4abf4b8b770f a sphn:LibraryPreparation ;
    sphn:hasDataProvider resource:CHE-101-064-173-DataProvider-2f2ace5d-d0e4-4d7c-aec7-2840b8d2b5d1 ;
    sphn:hasPreparationKitCode resource:Code-FG-Sample_preparation_Library_preparation_kit_Illumina_TruSeq_DNA_PCR-Free ;
    sphn:hasSourceSystem resource:CHE-101-064-173-SourceSystem-d1c3a94c-245d-4395-8f7a-a5db899c5abe .

# QualityControlMetric
resource:CHE-101-064-173-QualityControlMetric-018259e2-2516-4251-9792-f27132a0922d a sphn:QualityControlMetric ;
    sphn:hasCode resource:Code-GENEPIO-0000089 ;
    sphn:hasDataProvider resource:CHE-101-064-173-DataProvider-2f2ace5d-d0e4-4d7c-aec7-2840b8d2b5d1 ;
    sphn:hasQuantity resource:CHE-101-064-173-Quantity-b6fb26bb-7d55-41dd-9cdb-dcbfb4ed4913 .

# QualityControlMetric - phred score
resource:CHE-101-064-173-Quantity-b6fb26bb-7d55-41dd-9cdb-dcbfb4ed4913 a sphn:Quantity ;
    sphn:hasUnit resource:CHE-101-064-173-Unit-9c874e82-bb35-4742-8369-7a5027b89d08 ;
    sphn:hasValue "78.33"^^xsd:double .

# Standard Operating Procedure
resource:CHE-101-064-173-StandardOperatingProcedure-2f788f50-125d-48e8-a50b-3997a7a3ad09 a sphn:StandardOperatingProcedure ;
    sphn:hasDescription "SOP for WGS with the Illumina NovaSeq 6000"^^xsd:string ;
    sphn:hasName "WGS with Illumina NovaSeq 6000"^^xsd:string ;
    sphn:hasVersion "v2.1"^^xsd:string .

# Code
resource:CHE-101-064-173-Unit-7813741c-981d-4b6c-bbf6-a739eff4034d a sphn:Unit ;
    sphn:hasCode resource:Code-UCUM-cblnbcbr .

# Code
resource:CHE-101-064-173-Unit-9c874e82-bb35-4742-8369-7a5027b89d08 a sphn:Unit ;
    sphn:hasCode resource:Code-UCUM-percent .

resource:Code-SNOMED-CT-119297000 a snomed:119297000 .

resource:Code-EDAM-format_1931 a edam:format_1931 .

resource:Code-OBI-0002630 a obi:OBI_0002630 .

resource:Code-UCUM-cblnbcbr a ucum:cblnbcbr .

resource:Code-UCUM-percent a ucum:percent .

resource:Code-GENEPIO-0000089 a genepio:0000089 .

resource:Code-OBI-0002117 a obi:OBI_0002117 .
```

5. Discussion

A genomics semantic data model was developed that builds on the SPHN schema and follows a design that makes it applicable to other omics domains. The model covers clinical use cases from the SPHN NDSs including omics data from oncology, pediatric care, and pathogen surveillance and others at Swiss University Hospitals and research institutions. It aligns with common biomedical terminologies such as SNOMED CT, OBI, and GENEPIO, and mirrors the structure of existing domain models such as FAIR Genomes where possible. For instance, the pattern of expressing the investigative workflow as a sequence of processes, where material or data produced by one process serves as input for the next process, is similar to that of OBI and SIO. Also, the intended use of the genomics concepts mirrors that of FAIR Genomes, where FAIR Genomes' 'Sample Preparation' module broadly corresponds to the 'Library Preparation' concept, the 'Sequencing' module with the 'Sequencing Assay' concept, and the 'Analysis' module with the 'Sequencing Analysis' concept, respectively. The SPHN omics extension also reuses the value set for library kits from FAIR Genomes. In contrast to FAIR Genomes, we aimed for more normalization, for instance by introducing a separate 'Standard Operating Procedure' concept and reference it, while this information is part of the 'Material' and 'Analysis' modules as protocol attributes in the FAIR Genomes model. The 'Run' concept also served to factor out run-specific information, and keep all information that is the same for every run in a sequencing experiment within the 'Sequencing Assay' concept. In addition, we aim to use concept references over text or string attributes, such as with the 'Standard Operating Procedure', 'Software' (algorithm), or 'Quality Control Metric' concepts, all of which are expressed as text attributes in FAIR Genomes. Lastly, the SPHN omics extension for the SPHN RDF Schema offers several utility concepts, such as 'Isolate' and 'Gene Panel', that may be seamlessly combined with other concepts to express the clinical case metadata, has extension points to add additional concepts for any step in the omics workflow, and allows material or data processing concepts to be chained which allows for more fine grained expression of the experimental processing. Note that these differences are not shortcomings, but reflect the differences in application: where FAIR Genomes provides a generic content model for data capture applications for clinical NGS, the SPHN (gen)omics extension mainly focuses on semantic data exchange with a common framework to fit a broader range of omics fields. Data expressed using the SPHN RDF Schema may easily be transformed to the FAIR Genomes model, whereas the inverse is harder.

The model allows to describe metadata on the process, and, in combination with other SPHN concepts, the outcome of the genomics workflow. Bulk transcriptomics and, to a lesser extent, omics research in general can be represented with the model that is presented in this paper. Since the model is purely meant for exchange of experimental metadata and data, catalog-level metadata, such as study, funding, or attribution, was left out. Although there are some general purpose high-level concepts such as 'Sample Processing', 'Assay', and 'Data Processing', we refrained from introducing a complete concept hierarchy; only concepts that have direct applicability were introduced. Also, while it would be useful to allow for partonomy, for instance by allowing sample or data processing concepts to be composed of arbitrary part processes, it was deliberately not introduced in order to restrict to only one way to apply the concepts.

The 2023.2 SPHN RDF Schema release incorporated various external terminologies to enhance data description. For genomics, the following terminologies are provided on the DCC Terminology Service [16] Genotype Ontology (GENO), HUGO Gene Nomenclature Committee (HGNC), and Sequence Ontology (SO) for comprehensive variant representation and human gene naming. In the 2024.1 release, as genomics concepts expanded, additional terminologies such as EMBRACE Data and Methods (EDAM) ontology, Experimental Factor Ontology (EFO), Genomic Epidemiology Ontology (GENEPIO), and Ontology for Biomedical Investigations (OBI) will be integrated.

6. Conclusion

We developed a genomics extension of the SPHN RDF Schema, in close collaboration with stakeholders of the SPHN, to facilitate their data sharing use cases. This omics extension aligns with common biomedical ontologies and offers extension points for other omics research. This set of concepts forms the basis for the further concepts developed in the NDSs for other omics data, driving the vision of holistic view on the personalized health data in one single knowledge graph.

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