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2005B – Proposed Standards Artifacts (Medium) – Evaluation Plan

Solor Support Services: Use Case #3 Evaluation Plan

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A FORMATIVE EVALUATION OF THREE SOLOR EXTENSION USE CASES PROMOTING SEMANTIC INTEROPERABILTY
(CLIN 2005B_10.14, 2005B_11.14 and 2005B_12.14)

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VERSION HISTORY

DATE	VERSION	DELIVERABLE	DESCRIPTION
10/29/2018	0_0	Proposed Standards Artifacts (Medium)	Use Case
11/29/2018	0_1	Proposed Standards Artifacts (Medium)	Evaluation Plan
12/29/2018	0_2	Proposed Standards Artifacts (Medium)	Evaluation
1/29/2019	0_3	Proposed Standards Artifacts (Medium)	Manuscript Version
2/28/2019	0_4	Proposed Standards Artifacts (Medium)	Use Case
4/29/2019	0_5	Proposed Standards Artifacts (Medium)	Evaluation Plan
5/29/2019	0_6	Proposed Standards Artifacts (Medium)	Evaluation
6/29/2019	0_7	Proposed Standards Artifacts (Medium)	Manuscript Version
6/29/2019	0_8	Proposed Standards Artifacts (Medium)	Use Case
7/29/2019	0_9	Proposed Standards Artifacts (Medium)	Evaluation Plan

1   INTRODUCTION

The vision of the Department of Veterans Affairs (VA), Veterans Health Administration (VHA), Office of Informatics & Analytics (OIA), and Health Informatics (HI) is to provide timely, relevant information and data services that support improvements in Veterans' health. In meeting these goals, OIA strives to provide high quality, effective, and efficient information and data services to those responsible for providing care to the Veterans at the point-of-care as well as throughout all the points of the Veterans' health care in an effective, timely and compassionate manner. VA depends on the interoperability of information and data to meet mission goals. An essential step to achieving interoperability is the widespread adoption of clinical terminology standards, which are structured sets of codes and terms organized in hierarchies to represent and encode clinical concepts – including diagnoses, procedures, medications, administrative data, and laboratory results [1]. By 2020, adoption of certified Electronic Health Record (EHR) systems in the U.S. with data mapped to standard clinical terminologies is expected to approach 100%, due in part to EHR incentive programs created by the Health Information Technology for Economic and Clinical Health Act and Meaningful Use program [2].

Despite having such mandates, there are challenges in the application of controlled medical terminologies to clinical care that limit our ability to fully leverage EHR data to improve population health. Standard clinical terminologies are currently developed and delivered by various organizations in which the content is often created in silos, stored in different formats, represented by different models, and released with different cycles and mechanisms. As a result, end users of EHRs are taxed heavily to monitor, retrieve, implement, and analyze the ramifications of an update. This burden is compounded even further when a new set of content is required for use.

To this end, VHA's informatics architecture was created to integrate disparate knowledge sources and preserve the meaning of information for the interoperability of electronic health record data (i.e., semantic interoperability) which is critical for delivering safe veteran care and leveraging standards-based clinical decision support. The current complexity encountered by standards developers, authors, and implementers when trying to integrate disparate terminologies—and the lack of coherence between (and sometimes within) the terminologies themselves—must be overcome to build a foundation for scalable and extensible architecture. Solor, a system of logical representation, is the open source ecosystem of capabilities and services for overcoming these complexities by assimilating disparate health knowledge sources into a consistent representation based on best practices of computer science. Knowledge sources are integrated in Solor by transforming source terminologies into a common model that provides a uniform representation scheme and additional meta-data needed for semantic integration and advanced versioning. Users are able to navigate overlapping concepts, as well as the relationships between concepts. By doing this, Solor enables collaboration in health IT, unifies health terminology standards and removes ambiguity, leading to improved patient care.

1.1   Aims

The overarching objective of this body of work is to inform the development of Solor by exploring its extension as an ecosystem for integrating disparate knowledge sources and creating interoperability by making information meaningful and computable. The specific aims of this work are:

Aim 1: Develop use cases for the extension of Solor.

Aim 2: Evaluate constructs of the Solor use cases developed in previous aim.

2   BACKGROUND

An interoperable, integrated terminology model concerns (a) the foundation and building blocks of the common model; (b) how the transformation process of disparate standards into the common model is made repeatable and interoperable with other environments; and, (c) how the modules of the common model are tightly versioned controlled over time.

Solor is an ecosystem that allows users to import, transform, and view content from disparate medical terminologies, all in one common model. Users can navigate and search Solor content, view details of the data elements, and select specific concepts to view more information. As Solor is open-source, developers are encouraged to build on top of existing functionalities.

We adopted contemporary software principles to create a multi-layered architecture for integrating standard medical terminologies. We sought to adhere to three main principles in our architectural design: (a) to store concepts from medical terminologies so that one could apply classifiers and identifiers; (b) to allow for versioning and updates over time in a way that preserved concept orientation; and, (c) to promote collaborative, distributive workflows for developers.

2.1   The Solor System

Solor is an ecosystem that allows users to import, transform, and view content from disparate medical terminologies, all in one common model. Users can navigate and search Solor content, view details of the data elements, and select specific concepts to view more information. As Solor is open-source, developers are encouraged to build on top of existing functionalities.

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2.1.1   Building Blocks

Solor has two fundamental building blocks: concepts and semantics. Concept is defined as an idea or a general notion. When abstracted out, it can be used to represent any idea, whether that is a medically related idea (e.g., heart attack) or an idea to represent metadata (e.g., a synonym or a fully specified name). A semantic enables addition of semantic data to the underlying concept's content, in a standardized way that provides for the same means of identifying, modularizing, and versioning. In other words, a semantic is attached to a concept to provide contextual meaning to the concept. Semantics can be grouped together in a collection to form an 'assemblage'. An assemblage consists of semantics that reference a concept or semantic and provide additional data to that member for some purpose. Solor also has 'description semantics' with additional metadata specifying details including but not limited to 'language' and 'description type'. A logic graph semantic provides a property graph that represents a description logic statement (e.g., OWL 2 EL) for concepts.

2.1.2   Transformation Overview

After a standards developer releases its content, a process will need to occur to transform data from its native format into Solor components (e.g., concepts, semantics, assemblages). This programmatic process is tailored to each incoming data stream, where it will account for data represented in its

original format. Other than transforming and applying versioning coordinates, the underlying process will also address the notion of dependency. For example, SNOMED US Extension will have a dependency on SNOMED International, and relationships from the LOINC-SNOMED collaboration effort will have a dependency on SNOMED and LOINC. Once the content is in Solor, there is a step where equivalency is determined through various methods where concepts of the same idea are aggregated.

2.1.3   Identifiable Components

A universally unique identifier (UUID) is a 128-bit number used to identify information in computer systems. The identifiable component layer of Solor manages the reproducible assignment of UUIDs to all imported components (e.g., concepts, semantics, assemblages) as well as the assignment of primordial UUIDs to all internally generated components. If imported components already provide UUIDs to identify components, those UUIDs will be used. The identifiable component layer must allow components to have more than one UUID identifier, and if previously independent components are given each other's identifiers as alternate identifiers, the identifiable component layer must dynamically merge the parts of these previously distinct components into a single integrated component. This merging of components by merging identifiers is a simple means for managing duplicated content as it is identified.

2.1.4   Advanced Versioning and Modularity

An important design feature of the foundation for Solor's architecture is that it supports modularity – or the ability to allow for changes and sub-changes to be referenced uniquely. Modularity emphasizes separating the functionality of a program into independent, interchangeable modules, such that each contains everything necessary to execute only one aspect of the desired functionality. Solor's architecture is composed of multiple modules, and we refer to them as 'coordinates'. Each coordinate as defined below allows for optimal configuration of terminology management and allows for complex representations of content without burdening the end-users with having to deal with all aspects of the complexity themselves.

2.1.4.1   Versioning Coordinate

The chronology component of the architecture layer provides a means to generically represent the revisions to a component over time, and to index those revisions by status (e.g., active, inactive), effective time of change, author of change, module within which the change occurred (international edition, US extension, etc.), and the development path of the change (development, release candidate, etc.). Taken together, these fields can be referred to as a version's STAMP (status, time, author, module, and path). STAMP provides a foundation for version control and configuration management of all the components of the information architecture. The STAMP will provide a means to modularize content so that modules can be turned on and off depending on specific use cases, and that modular content can be developed independently from unrelated modules. This modularity will enable simplified development and quality assurance processes for each module. There are also more nuanced components within Status, Time, Author, Module, and Path that can be configured. These include: 'Allowed States' (related to Status), precedence, and the ability to specify groups of modules in a 'Module Set'. Precedence can be set to stratify the mathematical constructs surrounding the components (e.g., path, time) so that one component can be prioritized over the other. In summary, STAMP provides a high degree of configuration for navigating versions of content and how that

content may be interacted within the Solor ecosystem.

2.1.4.2 Language Coordinate

The language coordinate provides the ability to configure details around what language of content to provide, and to select a particular dialect, and/or the order of dialects available in the Solor ecosystem. This also provides the ability for users to get the exact level of granularity of content they desire.

2.1.4.3 Logic Coordinate

The logic coordinate allows configuration of description logics and formal knowledge representation of Solor content. The fundamental modeling concept is an axiom—a logical statement relating roles and/or concepts. Within the logic coordinate, users can specify which classifier to use (e.g., Snorocket), and which concepts they want to classify in their given use case (e.g., Solor content vs. Health content). Users can also specify how they want to configure the stated and inferred parent-child (supertype-subtype) relationships that are either available in the source terminology native logic, or through additional integration provided by the Solor common model.

2.2 Solor Knowledge Sources

2.2.1 Terminology Knowledge Sources

Terminology systems are increasingly critical components for achieving interoperability across applications in the healthcare domain. The role of standard terminologies in achieving interoperability for the purposes of advancing patient care is well documented [3]. Ideally, these clinical terminology standards intend to provide rules to allow for the exchange, integration, and management of electronic clinical information [4]. The federal government recognizes the benefit of standard terminologies and promotes their development and use. The Federal Health IT Strategic Plan 2015-2020 set a strategy to encourage consistent terminology standards implementation in Electronic Health Records (EHR) and encourage use through federal payment policies [5]. A standard terminology is one that has wide industry acceptance or use.

Standards are obtained from a variety of efforts, cover different domains of clinical and nonclinical content relevant to the EHR, and serve various purposes. Currently, no one terminology or classification system contains everything that is needed for the medical record. Examples of standard terminologies include:

- Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT®): a comprehensive clinical terminology, maintained by the International Health Terminology Standards Development Organization (IHTSDO) [6] representing over 300,000 concepts including disorders (22%), procedures (17%), body structures (11%), clinical findings other than disorders (10%), and organisms (10%) [7];

- Logical Observation Identifiers, Names, and Codes (LOINC®): a terminology representing about 50,000 clinical and laboratory observations, health measurements, and documents, developed and maintained by the Regenstrief Institute [8]; and

- RxNORM: a terminology for human clinical drugs in the U.S representing drug properties such as ingredient, strength, and dose form, maintained by the National Library of Medicine (NLM) and distributed via the Unified Medical Language System (UMLS) [9].

Terminology systems typically consist of the following elements:

- Coded Concepts – the discrete units of knowledge managed within the terminology. They typically consist of numeric codes and textual preferred names, synonyms, and descriptions.

- Concept Hierarchies – the logical organization of concepts into parent-child and ancestor-descendant relationships that express the semantics of generalization and specialization. The hierarchical organization of a terminology may be explicitly expressed through stored parent-child and ancestor- descendant links, or it may be implicitly expressed through the logical definitions of individual concepts that a computer can use to infer parent-child and ancestor-descendant relationships.

- Value Sets – named lists of individual concepts that represent more abstract categories useful in decision-support logic.

New applications and new medical knowledge constantly call for expansion and enhancement of existing terminologies. However, since terminology systems are often non-static, incomplete and under specified, inconsistencies may be introduced [10].

While many of these challenges are related to terminology evolution, others may be related to the design of the standard clinical terminologies themselves. Cimino notably described the challenges of concept orientation, completeness, correctness, currency, granularity, and redundancy when designing re-usable medical terminologies [11]. Today, 20 years later, a menagerie of inconsistent and overlapping terminology models hinders efforts that try to store and analyze encoded clinical data. Several efforts aim to assist. The National Library of Medicine (NLM) integrates terms and codes from over 150 source vocabularies by concept, attribute, and meaning in the Unified Medical Language System ® (UMLS) Metathesaurus. The NLM, also, in collaboration with the Office of the National Coordinator for Health Information Technology and Centers for Medicare & Medicaid Services, hosts the Value Set Authority Center (VSAC). The VSAC aims to provide lists of values, codes, and names (i.e., value sets) from standard clinical terminologies to represent clinical concepts.

These tools, while helpful, have gaps. Raje et al. highlighted issues with completeness, correctness, and redundancy when they found gaps in the UMLS Metathesaurus' coverage of disease concepts [12]. Similarly, Winnenburg et al. highlighted duplicate value sets in the VSAC, and showed that 19% of value sets in 2011 contained invalid codes [13]. In subsequent work, they highlighted issues related to granularity by evaluating over 1,000 value sets and found that value sets varied vastly in size with some only containing one code, while other value sets included over 20,000 codes (ref). Similarly, Bahr et al. showed issues with concept orientation by analyzing medication value sets and found extraneous and missing ingredients in both the value sets and drug classes [14].

These issues related to integrating clinical content have a direct impact on patient safety and point to the need to be able to consistently represent and encode clinical data and observations. Therefore, quality assurance is an indispensable part the terminology management lifecycle. A central limitation of integrating controlled medical terminologies is that they often lack any formal model to denote the relationships among constituent data elements.

Recently, however, development teams for SNOMED CT, LOINC, and RxNorm have partnered to promote interoperability. Developers can now leverage SNOMED CT's representation model for the building blocks of LOINC, and a new drug model in SNOMED CT facilitates extensions and consistency to RxNorm [7]. Bodenreider et al. wrote about the recent collaboration: "while this evolution leads to

greater compatibility and interoperability, integration of SNOMED CT, LOINC, and RxNorm still requires mappings among the three terminologies. Moreover, these three terminologies use different formalisms and tools for their representation, have their own release cycles and versioning mechanisms, which makes their seamless integration non trivial, if at all possible." [7].

2.2.2 Genome Variant Knowledge Sources

A key part of the work in the genome research domain is to identify genome variants and assign a clinical impact, if known. A genome variant knowledge source is a repository of known genome variants and associated clinical interpretations of that variant. There are many types of genome variant knowledge sources, which include (1) privately-controlled knowledge bases, such as the Human Gene Mutation

Database (HGMD) [15]; (2) open access, locus-specific knowledge bases, such as those created using the Leiden Open Variation Database (LOVD) [16]; (3) proprietary knowledge bases, typically owned and managed by genetic testing laboratories, who maintain exclusive access [17]; and (4) publicly available, centrally-managed repositories, such as ClinVar [18]. Typically, when a new variant is discovered, or new information about a known variant is made available, this information will be recorded in one or more of these knowledge bases. Furthermore, curators may monitor publications and reports in order to update a knowledge base accordingly.

ClinVar, which is a publicly available central resource managed by the National Library of Medicine, represents a model wherein genome knowledge sources can upload their expertly curated knowledge into one location [19]. Previously, genome knowledge consumers may have had to use several different genome variant knowledge bases and pay to access particular knowledge. Furthermore, with an open collaborative approach to genome variant annotation, ClinVar may become a more robust and extensive knowledge base than any single locus-specific or laboratory-managed knowledge bases. Open access, locus-specific knowledge bases tend to be curated and maintained on a volunteer basis, making the knowledge available limited. While laboratory-managed knowledge bases contain the best variant knowledge, they are also (1) limited by the number of unique variants observed by that laboratory and

(2) may have tightly controlled access to the variant knowledge in order to maintain a competitive advantage over other testing laboratories [17]. Nevertheless, if ClinVar is embraced by the diagnostic laboratory community with the support of the ClinGen effort [20], the laboratory knowledge bases will likely serve as one of the most important sources of variant annotations. Additionally, several characteristics of ClinVar make it attractive for our type of work:

Format – ClinVar maintains a health data repository available via FTP download in several release formats (e.g. TSV, XML, and VCF). In particular, the tab separated values release format, which provides data in a structure similar to relational database tables, is the easiest data format to be used in the Solor transformation process.

Documentation – Robust ReadMe files within each ClinVar release, describing in detail every data point contained within the overall ClinVar release data structure. Based on these descriptions, reliable inferences can be constructed for the Solor transformation process.

Release Cycle – Within the ClinVar release data tables, there exists variations (e.g. daily, weekly, monthly, etc) of update frequency amongst individual data entities. Variant data is updated weekly, whereas phenotypic data is updated daily. Creating a Solor transformation process around data

entities that are frequently updated results in more current variant data for the Solor system.

Data Structure – Specific data entities, such as variant, gene, and disease, can be normalized, modular, and isolated from other more complex entity relationships. These aspects for such key data entities result in a less complex, more straightforward implementation of the Solor transformation process.

Variant Identifier – ClinVar utilizes the Human Genome Variation Society (HGVS) specification for naming genomic variants contained within each release. Leveraging approved standards, as part of key data elements being transformed into the Solor system, enables proper terminology concept quality assurance and classifications to be performed on all Solor health data.

2.2.3 Clinical Laboratory and In Vitro Diagnostic Device Manufacturer Knowledge Sources

Clinical laboratorians provide information and services that contribute to maximizing the effective delivery of care in the healthcare system by assuring that the correct test is performed on the right person, at the right time. These services enable clinicians to make appropriate evidence-based diagnostic or therapeutic decisions for their patients. With the increased use of software systems in the health care environment today, it is now critical for laboratorians to install instruments that have the capability to efficiently exchange in vitro diagnostic (IVD) test results from a variety of settings (e.g., hospital-based laboratories, reference laboratories, physician office laboratories, home use testing, etc.).

Fundamentally, IVDs ask a question of a specimen taken from a human body, and the test result that follows is the answer to the question. Clinical laboratory and IVD knowledge sources include a repository of logical observation identifiers names and laboratory codes (i.e. LOINC) to vendor test results to encode these question-answer sets. To assist, The IVD Industry Connectivity Consortium (IICC) creates and encourages the adoption of unified connectivity standards, namely the digital format for publication of LOINC to vendor test results (LIVD) standards. Government mandates have required LOINC codes be used by clinical EHR vendors to encode laboratory results. Furthermore, information from IVD tests account for a significant portion of all EHR data. The LIVD specification assists laboratory personnel with the selection of appropriate LOINCs for their IVD test results that will eventually be sent to EHR systems. LIVD reduces variability in the mapping and maintenance of LOINC, reducing time and effort of laboratory professionals. The standard is also defined to allow Laboratory Information Systems (LIS) to automatically map IVD vendor test results to the appropriate LOINC codes and terms, thereby promoting semantic interoperability across the healthcare system.

The IICC in collaboration with the Food and Drug Administration (FDA) sponsored systemic harmonization and interoperability enhancement for lab data (SHIELD) workgroup, are working to pragmatically increase the adoption of the LIVD standard. IVD manufacturers are contributing to LIVD by publishing catalogs containing predefined LOINC codes that identify test results for their specific models and versions of devices. Subsequently, laboratorians consume these catalogs and use the LOINC codes to accurately represent and encode the test results in their LIS environments. While promising, current LIVD workflows are limited by (1) siloed publication mechanisms and lack of version control, with IVD manufacturers publishing their respective catalogs independently, and (2) significant burden in the time and cost required not only to author catalogs, but also to deploy, connect, and update laboratory instruments and software systems. Characteristics of the LIVD specification include:

Format – LIVD defines a table and digital format for its data specification. A spreadsheet is recommended as the table format. Spreadsheets can be used to filter the publication content as part

of a manual activity to select the LOINC codes. In addition, table content from multiple vendors can be merged into a single spreadsheet. JSON (JavaScript Object Notation) was selected as the digital format, and potential integration of the format schema with Fast Healthcare Interoperability Resources (FHIR) is in early development. Both the spreadsheet and JSON formats are compatible to be used in the Solor transformation process.

Documentation – The IICC maintains documentation about the data definition and structure of LIVD content.

Release Cycle – Within the IVD manufacturers publishing their own LIVD catalogs, there exists variations (e.g. quarterly, annually) of update frequency. Creating a Solor transformation process around the disparate catalogs that are frequently updated results in more current and consistent LIVD data.

LOINC –LOINC codes and attributes are also included within LIVD data catalogs. Leveraging standards-based terminologies, such as LOINC, can be facilitated in Solor by providing concept quality assurance and classifications to be performed on all Solor health data.

The current LIVD workflow is demonstrated in the image below.
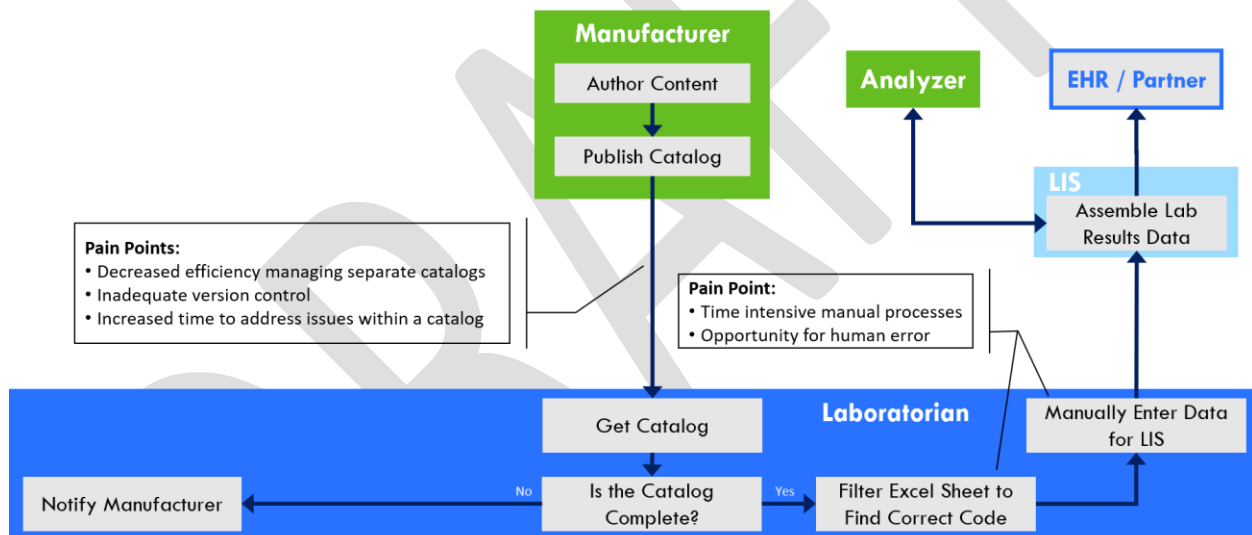
Figure 1: Current LIVD Process flow

2.3 Ecosystem

To be completed as part of future deliverable.

3 MATERIALS AND METHODS

3.1 Aim 1

3.1.1 Precision Medicine Use Case (CLIN 2005B_01.14)

Use Case 1 develops a Precision Medicine use case for Solor where variants which occur within genes are assessed for clinical impact using the curated genome variant knowledge base ClinVar. ClinVar, which is a publicly available central resource managed by the National Library of Medicine, represents a model wherein genome knowledge bases and laboratories can upload their expertly curated

knowledge into one location [19].

Genetic data knowledge sources are not structured or maintained in a format usable for the Electronic Health Records (EHR), clinical decision support, research, or interoperability despite the fact that precision medicine has become a national priority [Ref needed]. The market cost of genetic testing continues to decrease, while at the same time, the number of known genetic variants and number of genetic tests available continue to increase. Consequently, genetic information is becoming a more common addition to an individual's health records with important implications for treatment and research.

It is critical that individual genetic information is incorporated into electronic records in a consistent way so that clinicians and computer decision support systems (CDSS) alike can realize its benefits without errors or ambiguities. Accessible and standardized genetic-based test results and data sets have the potential to help clinicians provide better patient care if integrated into the electronic health record, enable more insightful population health statistics if in a standardized format and contribute to more impactful research if interoperable.

3.1.1.1 Genome Data Acquisition and Database Storage

The ClinVar knowledge source was added to the Solor ecosystem using a transformation process which allows for ClinVar specific data representation within the Solor ecosystem. Incorporating the ClinVar knowledge source into the Solor ecosystem required a custom implemented transformation process, which focused specifically on transforming the ClinVar tab separated value data format into the Solor common model format. Below describes the three data entities and the specific data elements used in the ClinVar to Solor transformation process:

Variant Summary – Contains attribute information that further describes gene variants submitted to ClinVar. The specific name of each variant in the HGVS format and the particular National Center for Biotechnology Information (NCBI) gene ID is used in the Solor transformation process.

Gene Specific Summary – Contains attribute information to further describe individual NCBI managed table of genes, specifically focusing on both gene's identifiers, the NCBI ID and its symbol data elements.

Gene Condition Source ID – Contains all relationships between genes and correlating diseases (phenotypes) used in ClinVar. This data entity contains not only the NCBI gene ID, but also identifiers of external phenotypic terminology concepts. For example, a specific gene ID is correlated with a potential SNOMED CT concept and the associated SNOMED CT Identifier (SCTID).

All variants and genes found in ClinVar were de-duplicated and loaded into the Solor model as unique Solor concepts. Each concept contained both a fully qualified name, based on either the variant's name and or the gene's symbol, as well as String identifiers that were based off the variant's HGVS ID, or the gene's NCBI ID. In addition, parent-child (supertype-subtype) relationships between concepts for variants to concepts for genes, and concepts for genes to SNOMED CT concepts, were encapsulated as logic graph axioms, visualizing a stated (modeled) view of the concepts as well as the view after classification, and assigned to each respective Solor concept. Lastly, a comprehensive Solor taxonomy was created incorporating both ClinVar and SNOMED CT concept.

3.1.2 Medical Device Interoperability Use Case (CLIN 2005B_02.14)

Use Case 2 develops a medical device interoperability use case for Solor in which it will serve as a central repository for facilitating LIVD specifications from device manufacturers to laboratorians. The IICC and FDA SHIELD are leading the collaboration amongst several stakeholders including federal agencies, IVD manufacturers, key healthcare systems, and international industry and standards-development groups. The specific aims of the LIVD specification are to facilitate the following model: (1) Vendor IVD tests results be associated with a set of predefined LOINC codes that identify the distinct observations produced by the test; (2) Observations with numeric values be associated with the UCUM representation of their reporting units; (3) Observations with categorical (multiple choice) values be associated with a response set that defined the possible values, with the response set drawn from appropriate code systems such as SNOMED CT. Figure 2 illustrates the proposed integration of the LIVD knowledge source and Solor.
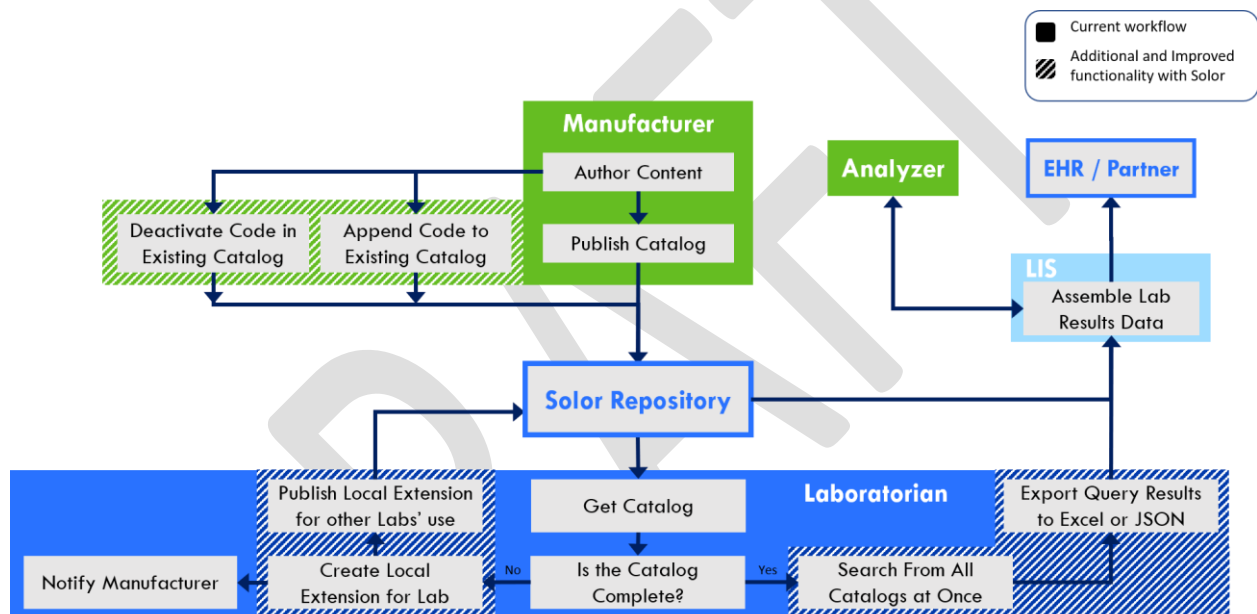
Figure 2: Proposed Integration of LIVD and Solor

The new standards bring about standardized coding of laboratory results and the resolution of semantic interoperability issues for the aggregation and exchange of health data, including for medical devices. In turn, these data standards support the promise of improved real-time epidemiology reporting, the analysis of population health data, and the analysis of multicorrelates that can lead to new discoveries. The result is overall cost savings to the public healthcare system.

3.1.2.1 Medical Device Data Acquisition and Database Storage

LIVD knowledge sources were added to the Solor ecosystem using a transformation process to represent LIVD data elements in the Solor common model. This required a custom implemented transformation process, which created components within Solor to transform and store the LIVD data format. All newly added LIVD data in Solor was then tied to pre-existing LOINC concepts in Solor to preserve the LIVD LOINC mappings. Below describes the three data entities and the specific data elements used in the LIVD to Solor transformation process:

Vendor Publication – Each catalog contains information about the publisher, versioning, and LOINC version used in the mapping.

Equipment – LIVD data contains specific data entities around the device manufacturer, models of devices, and unique device identifiers.

IVD Test Results – Values are aligned across manufacturers and device models with respect to: Vendor Analyte, Vendor Specimen Description, Vendor Results Description, Vendor Comments, and LOINC code.

All vendor publication, equipment, and test result data from LIVD were loaded into the Solor model as a multi-String type Semantic which were based off the LIVD data element's unique ID (e.g., device UID, Vendor Transmission Code), or the String description (e.g., Manufacturer Name, Vendor Result Description). These multi-String type Semantic Solor data elements were each included as a member of a grouping set (i.e., "assemblage") specifically created to store all of the LIVD data elements. Parent-child (supertype-subtype) relationships between Manufacturers to Device Models to IVD Tests were encapsulated as non-defining logic graph axioms, defining the view of the relationships between the LIVD data elements. We attach the LIVD multi-String semantic to a Solor concept which is also associated with the appropriate LOINC code as specified in LIVD catalogs.

3.1.3 HL7 FHIR Use Case (CLIN 2005B_03.14)

Use Case 3 develops a Health Level 7 International (HL7) Fast Healthcare Interoperability Resource (FHIR) use case for Solor in which it will serve as a FHIR extension that may have implications on FHIR terminology services. FHIR is an open, standards-based platform for medical apps designed to enable apps to connect to multiple EHRs. FHIR provides "resources" or detailed sets of references and core data models for application programming interfaces (APIs). FHIR describes a basic set of base resources and frameworks for APIs that can be used in many different contexts in healthcare. The FHIR specification allows for a variety of solutions to be implemented and often requires adaptation to particular contexts, including local terminology codes and content.

At present, FHIR does not attempt to address semantic interoperability and in 2013, Grahame Grieve the leader of the HL7 FHIR effort posted in reference to semantic interoperability: "let's not pursue the holy grail right now." [38] Rather than trying to address the additional complexity required for moving towards semantic interoperability, FHIR includes a base set of terminology resources that provides a broad framework for how implementers should address the use of standard terminologies. The Solor use case for FHIR will help provide a robust methodology for FHIR resources to deal with codeable concepts referenced within FHIR resources.

3.1.3.1 FHIR Resource Acquisition and Database Storage

The three primary FHIR terminology resources include:

Code Systems –This resource publishes lists of codes, where the codes can be related to definitions, so they have a known meaning. Some code systems are well known, such as SNOMED CT, LOINC, and RxNorm. Each code system in FHIR is identified by a system uniform resource identifier (URI) and an object identifier (OID).
Value sets – This resource provides selections of a set of codes defined by one or more code systems

for particular use.

ConceptMap – This resource provides static mappings between code system concepts in source and target value sets.

A FHIR resource that references a codeable concept may contain four properties to attach meaning to the concept of interest: 'code system', 'version', 'code', and 'display'. A shortcoming of FHIR's approach to handling terminology is that 'code system' and 'code' are the two minimally required elements to be included for codeable concepts, and all notions of versioning and synonymy may be lost in the current FHIR specification. As we have discussed earlier in this paper, there can be many codes used to define the same lab tests or diagnoses, and which specific codes are used may affect the interpretation of the clinical data by end-users. The Solor use case for FHIR will provide functionality to:

1. Import FHIR terminology resources, namely Code Systems, Value Sets, and ConceptMap

2. Query Solor data for better use of FHIR, including the ability to create and update terminology resources, searching Value Sets, and updating information about equivalency

3. Export Solor content to a FHIR format/specification, which improves FHIR terminology

FHIR resources were imported to the Solor ecosystem using a transformation process to represent FHIR resource and FHIR terminology data elements in the Solor common model. This required a custom implemented transformation process, which created components within Solor to transform and store the FHIR terminology data format. All newly added FHIR data in Solor was then tied to pre-existing concepts in Solor when possible to preserve the FHIR terminology concept mappings.

All FHIR terminology data elements were imported into Solor as multi-String type semantics and were based off the FHIR terminology data element properties (e.g., code system, code, version, display). These multi-String type Semantic Solor data elements were each included as a member of a grouping set (i.e., "assemblage") specifically created to store all of the FHIR terminology data elements. Concepts in Solor were given membership to a FHIR assemblage that has a string ID representing the OID and URI for the codesystem from the FHIR Code System Resource. We also created assemblages to represent the FHIR value set data elements from the FHIR Value Set resource including String-type semantics for the value set ID and sets of codes. Finally, a third type of assemblage with multi-String type semantics was created to represent the FHIR data elements from the FHIR ConceptMap resource to allow for the configuration of equivalence and dependencies of the data elements between and amongst code systems and value sets within the Solor ecosystem.

3.2   Aim 2 (CLINs 2005B_04.14, 2005B_05.14 and 2005B_06.14)

3.2.1   Evaluation Design

We will perform a formative evaluation of use case constructs – using a qualitative design. Formative studies are particularly useful for applied work, where it is more important to understand the process by which things happen in a particular situation than to measure outcomes rigorously or to compare a given situation with others [21]. Formative evaluation is a common approach for improving the quality of a program being developed by identifying weaknesses throughout the design and development efforts so that it will be as likely as possible to achieve the objectives for which it was designed [22,23]. A formative evaluation aims to help develop and improve programs from an early

stage, when opportunities for influence are likely to be greatest, and to identify promising components [24]. Innovative programs provide an ideal environment for use of formative evaluation findings, with key stakeholders generally much more willing to make adjustments at an early stage than when a program is well established [25].

The goal of this formative evaluation is to collect rapid feedback from subject matter experts that would provide validation of use case constructs and context for future successive adaptations and improvement of the use case's development. Having said that, key questions for evaluating a new proof-of-concept include: Does the idea provide a new and more useful capability?; does it help developers better understand complex systems?; and does it demonstrate by its behavior that a complex assembly of components can accomplish a particular set of activities? Our formative evaluation research questions are shown in Table 1.

3.2.2 Evaluation Participants

We combined both purposeful expert sampling and snowball sampling to create an interview strategy to gather knowledge from individuals that have particular expertise[26,27]. We first identified key informants (someone knowledgeable about health informatics) to begin the process of interviewing and we then asked for the names of subject matter experts (individuals especially knowledgeable and experienced with medical terminological systems). In addition, it was also important that participants were available and willing to contribute, and able to effectively communicate their experiences.

3.2.3 Methods Used for Data Collection

This work will use as its primary data gathering method a semi-structured interview approach, as described by Steinar Kvale in Doing Interviews [28]. It's a fairly open approach where a guide is used, with questions and topics to be covered. The evaluator has some discretion with the order in which questions are asked, but the questions are standardized, and provided to ensure that the researcher covers the correct material. Unlike the structured interview where the questions are fixed and they are asked in a specific order, questions or topics can be further developed on the basis of responses from the interviewee. Semi-structured interviews allow for in-depth encounters in which focused, conversational, two-way communication is used to elicit detailed narratives and are often used by evaluators wanting to delve deeply into a topic and to thoroughly understand the answers provided.

This approach aligns with the approach for conducting semi-structured interviews described in the RAND Corporation report "Data Collection Methods: Semi-structured Interviews and Focus Groups" [29]. An overview of the important aspects of semi-structured interviews includes a number of steps. First, the main research questions need to be identified. In other words, what does the researcher hope to learn? Next, the researcher needs to consider the different participant types and determine the sampling. This study used judgment/purposeful sampling where individuals were selected based on their knowledge of medical terminologies, and because their opinion was judged to be important to the research [27].

Interviews are typically personal and intimate encounters that allow for focused, conversational, two-way communication in which open, direct, verbal questions are used to elicit detailed narratives and stories[30]. This study conducted semi-structured interviews where an interview is defined as: a method of data collection in which one person (an interviewer) asks questions of another person (a respondent) either face-to-face or by telephone[31]. Although no interview can truly be considered structured, they were relatively structured and more or less equivalent to guided conversations.

We engaged participants at a single point in time, individually, using virtual meeting software, and conducted open-ended, semi-structured interviews. Participants were contacted by email to invite them to participate and a meeting time was then set at a time and day of their convenience. The total time was allotted no more than two hours for the investigators to complete the interactions. Participation in this study was voluntary and the subject matter experts could choose not to take part in the interview. The subject matter experts could also skip any question they preferred not to answer or terminate the interview without penalty. We asked each participant four demographic questions: (1) job title, (2) number of years of experience, (3) education level and (4) previous terminology experience. All demographic data gathered about the participant were free text.

3.2.4 Methods Used for Data Analysis

Applied thematic analysis, a method for identifying and analyzing patterns of meaning in a dataset, was used to organize and describe the data collected from the interviews [32–34]. Applied thematic analysis provided a rigorous, yet inductive, set of procedures designed to identify and examine themes from textual data in a way that is transparent and credible [35]. The procedure for performing an applied thematic analysis had the following steps: (1) collect data, (2) transcribe conversations, (3) list patterns of experience, which can come from direct quotes or paraphrasing common ideas, 4) identify data that relate to already classified patterns, (5) combine and catalog related patterns into themes, and (6) formulate theme statements and develop a summary of findings.

3.2.5 Precision Medicine Use Case

A prioritized subset of our precision medicine use case formative evaluation questions and semi-structured interview questions are shown in Table 1 and Table 2, respectively. See Appendix 1 for the full Precision Medicine Interview Guide. The questions may have been modified in light of what is learned during the interview and to fit the expertise of the interviewee.

Table 1: Precision medicine use case formative evaluation questions

Use Case Construct	Formative Evaluation Questions
Knowledge Source(s)	What are the publicly available (domestic or international) non-proprietary sources of information for Genome Variant – Clinical Impact knowledge?
Solor System Integration	Does the integration of ClinVar into the Solor System seem to be a sound and reasonable approach for promoting genomic data set use in a clinical setting?
Relevance	Does our work contribute to advancing precision medicine and genotype-phenotype interoperability?

Table 2: Precision medicine use case semi-structured interview questions

Use Case Construct	Semi-Structured Interview Questions
Knowledge Source(s)	• Is the ClinVar knowledge source used in our use case a valid knowledge source? • Are there any additional sources that could be utilized? • Are there any sources that should not be utilized? If so, why not?
Solor System Integration	• Do you think this approach to integrating the ClinVar knowledge source is reasonable?
Relevance	• Does this use case advance genomic interoperability? • How might this use case be extended and generalizable?

Three experts were identified and recruited to participate in semi-structured interviews for the

formative evaluation of the precision medicine use case. Experts were contacted who had experience working with NIH/NCBI genomics datasets, precision medicine and data science initiatives, redesign of clinical service programs, molecular biology, diagnostics, and infectious disease. The precision medicine use case expert population of interest has the following profile:

-Technically trained in biomedical informatics, precision medicine, and/or genomics
-Experienced with implementing and/or developing genomics knowledge sources
-Familiar with gene, variant, and disease terminology specifications

3.2.6 Medical Device Interoperability Use Case

A prioritized subset of our precision medicine use case formative evaluation questions and semi-structured interview questions are shown in Table 3 and Table 4, respectively. See Appendix 2 for full Interview Guide. The questions may have been modified in light of what is learned during the interview and to fit the expertise of the interviewee.

Table 3: Medical device Interoperability use case formative evaluation questions

Use Case Construct	Formative Evaluation Questions
Knowledge Source(s)	What are the publicly available (domestic or international) non-proprietary sources of information for device manufacturers and laboratories?
Solor System Integration	Does the integration of LIVD data into the Solor System seem to be a sound and reasonable approach for promoting medical device data set use in a lab setting?
Relevance	Does our work contribute to advancing medical device data and lab data interoperability?

Table 4: Medical device interoperability use case semi-structured interview questions

Use Case Construct	Semi-Structured Interview Questions
Knowledge Source(s)	• Is the LIVD knowledge source used in our use case a valid knowledge source? • Are there any additional sources that could be utilized? • Are there any sources that should not be utilized? If so, why not?
Solor System Integration	• Do you think this approach to integrating the LIVD knowledge source is reasonable?
Relevance	• Does this use case advance medical device and laboratory interoperability? • How might this use case be extended and generalizable?

Three experts will be identified and recruited to participate in semi-structured interviews for the formative evaluation of the medical device interoperability use case. Experts were contacted who had experience working with medical device manufacturer data, clinical laboratorian data, laboratory information systems, molecular biology, diagnostics, and public health data. The medical device interoperability use case expert population of interest has the following profile:

-Technically trained in software, clinical informatics, molecular biology, and/or diagnostics
-Experienced with implementing and/or developing laboratory-encoded data from medical devices

-Familiar with the authoring/developing/implementing terminological specifications from medical device manufacturers, clinical laboratorians, and LOINC.

3.2.7   HL7 FHIR Use Case

A prioritized subset of our HL7 FHIR use case formative evaluation questions and semi- structured interview questions are shown in Table 5: HL7 FHIR use case formative evaluation questionsTable 5 and Table 6, respectively. See Appendix 3 for full Interview Guide. The questions may have been modified in light of what is learned during the interview and to fit the expertise of the interviewee.

Table 5: HL7 FHIR use case formative evaluation questions

Use Case Construct	Formative Evaluation Questions
Knowledge Source(s)	What are the publicly available (domestic or international) non-proprietary FHIR terminology services?
Solor System Integration	Does the integration of FHIR resources into the Solor system seem to be a sound and reasonable approach for promoting FHIR use in a clinical setting?
Relevance	Does our work contribute to advancing FHIR resource interoperability?

Table 6: HL7 FHIR use case semi-structured interview questions

Use Case Construct	Semi-Structured Interview Questions
Knowledge Source(s)	• Is the FHIR terminology service used a valid knowledge source? • Are there any additional FHIR terminology services that could be utilized? • Are there any FHIR terminology services that should not be utilized? If so, why not?
Solor System Integration	• Do you think this approach to integrating the FHIR resources is reasonable?
Relevance	• Does this use case advance FHIR resource interoperability? • How might this use case be extended and generalizable?

Three experts will be identified and recruited to participate in semi-structured interviews for the formative evaluation of the HL7 FHIR use case. Experts were contacted who had experience working with FHIR resources and terminology services. The HL7 FHIR use case expert population of interest has the following profile:

-Technically trained in software, clinical informatics, and/or FHIR terminology services
-Familiar with FHIR resources and FHIR terminology services
-Experience working with RESTful Application Program Interfaces (APIs) and JavaScript Object Notation (JSON)
-Extensive knowledge surrounding clinical terminology standards

4   RESULTS

To be completed as part of future deliverable.

4.1 Precision Medicine Use Case (CLIN 2005B_07.14)

4.1.1 Participants

We interviewed three individuals with the participant characteristics described in Table 7. Participants had leadership and technical roles with 15-20 years of experience and were subject matter experts in the domain of precision medicine with knowledge of healthcare standards, terminologies, knowledge commons and genomic databases. All subjects had experience with precision medicine, ranging from 1 to 13 years, mean of 5.67 years.

Table 7: Participant Characteristics

Participant	Job Title	Professional Experience (years)	Education Level	Precision Medicine Experience (years)
1	Senior Manager	15	MS	3
2	Executive	20	PhD	13
3	Specialist Leader	15	PhD	1

Participant 1 had a wealth of knowledge related to technological health care solutions. After a career as a general nurse practitioner and public health professional, she shifted focus to Health Informatics where she has worked on electronic health record transformation as well as the development of software solutions to solve life science and health care problems. Recently, she has led National Institute of Health (NIH) health strategy and analytics projects. She did not have any specific experience with genomic data.

Participant 2 was well versed in the field of genomic data. He first started working at the NIH nearly 20 years ago on an intermittent basis but has been working full time on various NIH projects for the last 13 years. Due to his work experience with the National Cancer Institute (NCI), he has a large amount of experience specifically with genomic data. Through this work, he is familiar of the idea of using genomic data for precision and personalized medicine.

Participant 3 had a wealth of clinical research experience. She has been involved with biomedical research for over a decade during her PhD and postdoc years. She has experience at NIH as well as years of experience in the research and clinical trial arena with Military Health Systems (MHS). Furthermore, due to her background with molecular biology, she has research experience manipulating the promoter and enhancer regions of a gene with a pharmacologic perspective.

4.1.2 Semi-Structured Interviews

Between November 1st and November 30th 2018, we performed three semi-structed interviews. The interviews were facilitated by the Use Case Development team. Virtual meetings were arranged at times convenient for all three attendees. There was an interview presentation to guide the conversation that included slides on Solor background, genomic-phenotype motivation, ClinVar knowledge source approach, and its integration with the KOMET GUI prototype. Each participant was asked the interview questions shown in Table 2. Interviews lasted approximately 30 minutes. These semi-structured interviews were based on components from the PRECEDE-PROCEED model [36] to identify key information about each expert's background, experience with ClinVar/ genomics data, and their insights about Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis

and Evaluation (PRECEDE), and Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development (PROCEED) – in the precision medicine environment. PRECEDE involves assessing community factors by determining the social problems and needs of a given population, the determinants of an identified problem, as well as the behavioral and environmental determinants that predispose, reinforce, and enable certain behaviors [36] PROCEED involves the identification of outcomes and implementation by assessing availability for resources, whether certain programs are reaching intended populations, and evaluating behaviors based on incidence of negative/positive behaviors [36].

4.1.3 Applied Thematic Analysis

We performed an Applied Thematic Analysis [34]. We conducted the analysis concurrently to data collection; we continually examined and analyzed the data in an attempt to identify and articulate patterns or themes noticed during the interviews. Our analysis involved a constant iteration between interview data, coded transcript extracts and the forming themes. Writing was an integral part of the analysis lifecycle, beginning with the jotting down of ideas and through the analysis process.

In the first step, we familiarized ourselves with the data. The interview audio recordings were transcribed into text document transcripts. We immersed ourselves in the data by repeatedly reading and rereading the interview transcripts, searching for meaning and patterns and becoming familiar with the breadth and depth of the content. Next, an initial list of codes was generated from the transcript of what appeared to be an interesting feature in the data, where codes refer to the most basic element of raw interview data [37]. We organized codes into validation and recommendation statements supported by participant interview excerpts, or snippets, as shown in Table 8, and patterns across the interview data began to form.

Table 8: Summary of understanding of interview data

Construct	Validation	Recommendation	Participant Excerpts (Snippets)
Knowledge Source(s)	The presented knowledge source(s) is a good source for the precision medicine use case.	• Seek a more authoritative answer from individuals who may have more knowledge of specific databases.	• "ClinVar is a great first stop to find genomic data" • "I can connect you with some people that could probably answer .. what other data sets .. that you should be looking into."
Solor System Integration	The integration of ClinVar and clinical terminologies seems reasonable.	• The current integration effectively shows the connections between variants, genes, and disorders. • Get an early adopter for better guidance.	• "Seems like this will be extremely useful for physicians to see these relationships [between genes, variants, and disorders]" • "Get an early adopter to pick it up fairly quickly so you can get better guidance on whether it's useful and whether the user interface offers something to them that helps them make a decision."

| Relevance | This type of work can move precision medicine interoperability forward. | • This is useful for preventative medicine.
• Include information on the correlations between genes.
• Show the relationships between genomic data and treatment plans. | • "Really useful for a physician to be able to take a look at what came back and use it to inform preventative measures or suggest lifestyle changes"
• "Correlations like [those between genes on the same locus] will be extremely useful for physicians in making clinical decisions"
• "my next question is… how do I use it for determining the right treatment for the patient?" |

Next, patterns were organized to a broader level of summary of findings that captured something important about the data or meaning within the data set, as shown in Table 9.

Table 9: Summary of findings of interview data

Construct	Context Related to Materials & Methods	Summary of Findings
Knowledge Source(s)	We use a publicly available knowledge source called ClinVar which is available through the National Library of Medicine. ClinVar reports the relationships between human variations and phenotypes .	ClinVar is an appropriate starting point and valid to demonstrate the value of this use case. However, more research must be done to validate the use of the ClinVar knowledge source compared to other existing genomic data sets.
Solor System Integration	We integrated a knowledge source into the Solor platform and created a common model, allowing for a ClinVar specific data representation within the Solor ecosystem.	The ClinVar knowledge source has been successfully integrated into the Solor platform to effectively demonstrate the connections between genes, variants, and disorders. However, to continue to improve the Solor tool in this use case, it is important to get an early adopter to being using this tool in a real-world setting.
Relevance	The integration of the ClinVar data source into the Solor model can be used to increase precision medicine interoperability.	The precision medicine use case of Solor has many potential improvements that will make it more clinically useful. These include, but are not limited to, treatment plan support and gene correlations.

For the final step, themes were developed that represent something important about the data in relation to the evaluation question. The following themes emerged:

- **Theme**: More research needs to be done to ensure the correct knowledge source is selected.
  - ○ **Subtheme**: ClinVar is a good starting point, and demonstrates the potential of this precision medicine use case.
  - ○ **Subtheme**: There are many data sets available. Seek guidance from someone who has more knowledge related to the type of knowledge sources that exist.

- **Theme**: The precision medicine use case must be expanded to think about how it can support clinical decision making.
    - o **Subtheme**: We can incorporate more information into the taxonomy tree to help with this clinical decision support, including treatment plan support and gene correlations.
    - o **Subtheme**: Get input from clinicians to better guide the development of this use case.

4.1.4 Findings Summary

The goal of the semi-structured interview process was to evaluate key constructs of our Solor precision medicine use case. The results from the first construct, knowledge source, were broadly positive. Interviewees could easily conceptualize how ClinVar might inform the understanding of a genotype-phenotype knowledge use and how there might be additional resources that could be leveraged to assist in this understanding.

The subject matter expert who seemed to have the greatest knowledge related to the ClinVar data set stated that it is a good source to find information mapping genotypes to phenotypes. However, he did caution that his expertise is in the research realm, while the application of the precision medicine use case is geared more directly toward clinical decision support. He could not confidently say if there were other data sets available that are more applicable to clinical decision support. Consistent across the three subject matter experts was the sentiment that with that vast amount of available data, many data sets can and should be considered. ClinVar seems to be a viable option and good starting point, however our subject matter experts were unable to confirm that it was the "best" data source for the precision medicine use case. Therefore, more research must be done before this can be taken toward a fully usable product capable of improving patient safety and clinical decision support.

Furthermore, the subject matter experts each reported some findings and opinions in terms of how this precision medicine use case can assist clinical decision support. Each subject matter expert shared the opinion that this seems to be an extremely effective way to view and analyze the connection between genes, variants, and diseases as well as the associated SNOMED CT code. Several of the subject matter experts agreed that this already lends itself to the application of preventative medicine, which aligns nicely with the recent trend of a focus on preventative medicine present throughout the medical field. However, given the ability of the precision medicine use case to demonstrate the relationships between genes, variants, and diseases, there are several improvements that can be made to facilitate a more effective and useful tool.

With the idea of clinical decision support in mind, the precision medicine use case can be taken one step further to include treatment plans. Currently, the precision medicine use case utilizes Solor to effectively provide information to a clinician regarding the various genes related to a disease, but it does not give any guidance on how treatment can be personalized based on that individual's genome. The precision medicine use case lends itself to include efficacy of treatment plans for specific gene types. This would likely include the utilization of another data source, so the subject matter expert suggested the involvement of a data scientist who could help ensure that the data is consumed properly while being imported into the Solor taxonomy tree.

Additionally, another extension to consider for our precision medicine use case that would assist a physician in clinical decision support, is the ability to connect genes that are correlated to each other. Often, a genetic mutation in one area can affect the entire gene locus, essentially causing a ripple effect and increasing the likelihood of other conditions that are associated with other genes on that same locus. An example given by one of the subject matter experts was the idea that an individual with an underbite may be more prone to developing a heart murmur, due to the genes associated

with these disorders sharing a gene locus. Understanding these correlations would be extremely useful for physicians as they make clinical decisions. Once again however, this type of extension to the precision medicine use case would likely involve the integration of another data source.

Overall, an early adopter at NIH should be identified to collaborate on the precision medicine use case of Solor. The subject matter experts provided encouraging feedback about the ability for this use case to assist in improving patient safety and clinical decision support. The precision medicine use case to date has showed the ability to effectively form relationships between genotypes and phenotypes. This can immediately have an impact on certain preventative medicine measures. Additionally, it has the ability to be extended into a more robust model that can influence clinical decision-making processes by giving physicians extensive information not only about efficacy of treatment plans among genetic populations but also about gene-to-gene correlations and their effect on phenotypic likelihoods. Because it has been demonstrated that this use case can be useful, it is paramount that an early adopter is identified to begin interacting with the Solor tool in a clinical environment. This will provide meaningful feedback from a physician's perspective, resulting in an effective and useful tool that assist clinical decision support and in turn improve patient care.

4.2 Medical Device Interoperability Use Case (CLIN 2005B_08.14)

4.2.1 Participants

We interviewed three individuals with the participant characteristics described in Table 10. Participants had leadership and technical roles with 19-26 years of experience and were subject matter experts in the domains of medical devices, diagnostics, therapeutics, and drug discovery. All subjects had experience with medical device data, ranging from 19 to 26 years, with a mean of 21.67 years.

Table 10: Participant Characteristics

Participant	Job Title	Professional Experience (years)	Education Level	Medical Device Experience (years)
1	Informatics Software Architect	20	PhD	20
2	Specialist Leader, Drug Discovery	26	B.S / MBA	26
3	SME in In Vitro Diagnostics	19	PhD	19

Participant 1 has a wealth of knowledge related to diagnostic instrumentation inside the lab itself, and fully understands the type of information that diagnostic devices need to function as well as how diagnostic devices transmit data. He is also extremely familiar with LIVD as he was a part of the development of the LIVD specification and most of his work has been focused on bringing the next generation of device connectivity.

Participant 2 has a background in drug development, biotech, pharma, and academic research. He currently works with the Oncology Center of Excellence within the FDA, specifically focusing on product labelling using publicly available evidence. While he is not familiar with the LIVD specification, he does have experience in the laboratory industry.

Participant 3 is extremely familiar with the SHIELD effort to facilitate interoperability for medical device data. He has a background in molecular microbiology, as well as in imaging. A background in microbiology eventually led to him reviewing diagnostics as well as interacting with instrumentation

and software. He completed post-doctorate training in the bio-materials division of the National Institute of Standards and Technology where he developed therapeutics and reviewed the efficacy of these therapeutics. It was during the design of efficacy for therapeutics in which he started to work in the realm of clinical informatics. After becoming involved in the informatics space, he has been involved in the creation of SHIELD to help address the issues with medical device interoperability including the adoption and authoring of health IT terminology standards.

4.2.2 Semi-Structured Interviews

Between May 21st and May 24th, 2019, we performed three semi-structured interviews. Using the semi- structured interview framework, the Use Case Development team followed an interview presentation to guide the conversation that included slides on Solor background, LIVD specification background, our approach for integrating LIVD data into Solor and a demonstration of how imported LIVD data looks in the KOMET GUI prototype.

4.2.3 Applied Thematic Analysis

We performed an Applied Thematic Analysis [34], as described in 4.1.3 and summarized interview patterns below in Table 11.

Table 11: Summary of understanding of interview data

Construct	Validation	Recommendation	Participant Excerpts (Snippets)
Knowledge Source(s)	The presented knowledge source(s) is/are a good source for medical device interoperability.	LIVD was created because it aims to fill the gap of medical device data interoperability. No other data sources have been created for vendors to transmit codes in this manner.	• "No other standard exists for vendors to transmit code" • "I am not aware of anything else" • "Other international standards may exist for identification of lab results"
Solor System Integration	Solor's integration of LIVD seems to preserve all information provided in the spreadsheet.	Solor currently consumes and integrates LIVD data effectively. However, we should continue to refine workflow processes for device manufacturers.	• "Representation of the LOINC mappings clearly aligns with the approach we took with IICC." • "In essence you are providing a similar filtering capability that we were initially trying to produce with excel filtering" • "How does this benefit someone from a business or clinical care standpoint? How does this drive more efficient care?"
Relevance	This type of work can move medical device interoperability forward.	There will need to be some policy changes surrounding Solor to ensure that it becomes more than just an academic tool.	• "Regulators need to make this a required activity rather than an academic exercise." • "We have the right manufacturers and software manufacturers involved, but device manufacturers and laboratories need to drive the adoption rather than the manufacturers and the software developers."

Next, patterns were organized to a broader level of summary of findings that captured something important about the data or meaning within the data set, as shown in Table 12.

Table 12: Summary of findings of interview data

Construct	Context Related to Materials & Methods	Summary of Findings
Knowledge Source(s)	We used a medical device data set called LIVD, which is made available by medical device manufacturers. The LIVD specification reports the relationships between medical device tests and the associated LOINC codes.	LIVD is the only data source that aims to address the problem of medical device data interoperability. Therefore, this is the correct data source to be using in Solor.
Solor System Integration	We integrated the LIVD data set into the Solor common model, and represented the LIVD data within Solor in a similar way to the original data provided..	The LIVD data can be effectively consumed into the Solor model and displayed appropriately. Initial integration efforts centered on importing the LIVD specification, creating a LIVD assemblage, exporting the LIVD assemblage and edited content, and providing the ability to edit LIVD content. .
Relevance	The integration of the LIVD data source into the Solor common model can be used to increase the effectiveness of the LIVD specification and therefore improve medical device interoperability.	Solor can drastically improve the usability of LIVD and make it a lasting solution for medical device data interoperability. To do this, Solor needs to continue to develop features that allow it to fit into the manufacturer workflow.

For the final step, themes were developed that represent something important about the data in relation to the evaluation question. The following themes emerged:

- **Theme**: The LIVD data source is the best specification to represent the relationships between medical device tests. This includes the analyte and specimen details, and the associated LOINC codes in clinical and laboratory information systems.
  - o **Subtheme**: LIVD is the only known knowledge source that advances medical device and laboratory data interoperability.
- **Theme**: The LIVD data can be effectively consumed into Solor and displayed appropriately. The use of this data still needs to be operationalized, with additional advanced features.
  - o **Subtheme**: Solor needs to continue to develop the following features to increase the effectiveness and usability of the LIVD specification: Authoring (creating/editing content), Version Control and Advanced Querying (Reconciling between versions of the same data elements), and fitting into a RESTful workflow.

4.2.4 Findings Summary

The results from the evaluation process of the LIVD integration into Solor were broadly positive. The interviewees were not aware of any knowledge sources other than LIVD that provide the necessary information to make semantic interoperability between medical devices and laboratories possible.

The experts agreed that LIVD is an appropriate knowledge source for improving medical device and laboratory interoperability and believe there are no alternative data sources to consider.

Despite varying perspectives and areas of expertise with the medical device industry, all three participants tended to agree on two topics. First, the resources acting as enabling factors for enhancing medical device interoperability. Second, the challenges that act as barriers to clearly preserving semantic meaning between medical devices, laboratories, and clinical care. Fundamentally, existing medical terminology standards were mentioned as enabling factors. SHIELD has identified key opportunities to solve "the low hanging fruit of interoperability" addressing gaps regarding the effective use of widely adopted standards such as LOINC and SNOMED CT. One challenge mentioned was the unique and non-overlapping nature of workflows, needs, and pain-points/barriers for each SHIELD stakeholder; the device manufacturers have their challenges authoring the LIVD catalogs, while laboratorians struggle to retrieve the correct versions and manually configure their information systems. The SHIELD solution and the LIVD specification aim to aid semantic interoperability across the board irrespective of the end-user at the authoring or implementing phase of the workflow.

All three participants tended to agree that the Solor integration of the LIVD specification was valid. In fact, two of three interviewees indicated that our representation of LIVD was similar to the original flat file representation of the LIVD catalog data, while one interviewee indicated that Solor does a lot more than the basic filtering and sorting offered by Microsoft Excel. In particular, the ability of Solor to create concepts as extensions to standard medical terminologies was named as part of the context that Solor "has to make it a very powerful tool". In the current Excel process, if there is a null value for a LOINC code, then implementers of the LIVD specification are stuck, or forced to make their own local decisions/definitions in silos, until a new version of that LIVD catalog is released. With Solor extensions, implementers can create Local definitions and share them via Github with the authors and other implementers – thereby promoting an interim shareable concept, or LIVD extension. This LIVD extension concept may eventually become a part of the LIVD specification if other stakeholders collaboratively agree with the concept's intent and usage. Another key feature of Solor highlighted as beneficial was the advanced version control of data elements. Currently, it is not clear if an entire row of data in a current LIVD catalog is updated. Within Solor, the row could be given a UUID, and any updates over time could be pinpointed for the user to analyze. Furthermore, any updates to LOINC, and eventually SNOMED CT, would also be tracked within the Solor ecosystem, reducing the burden on the authors and implementers of the LIVD specification to not only track the authoring and evolution of their own content, but also that of other derivative standards.

When shown the initial build of the LIVD integration in the Solor GUI, most participants did not report that the build or integration was readily confusing or ambiguous. Participants tended to agree that the LIVD representation in the Solor GUI was easy to understand and represented the LIVD data elements and relationships between manufacturers, devices/products, analytes, specimens, results, and the corresponding LOINC code. However, the participants had differing perspectives regarding the degree to which Solor's functionality improved the overall usability of the LIVD specification.

From one interviewee's perspective (on behalf of the device manufacturers), it was not clear how much value was being added by Solor's ability to represent unique ID's for rows of data. It was also not clear to the interviewee why a high level of version control might be needed, or what the additional benefit is for the authors of LIVD content (device manufacturers). This same interviewee also expressed that it may not be actionable to increase the representation of ordinal and nominal variables currently expressed in LIVD as strings by encoded values from LOINC or SNOMED CT. However, the other two interviewees understood the value added by Solor. One of the participants said "the LIVD spreadsheet has never been intended to be that long term living resource. It was meant

to be fed into something robust like Solor that can actually control all that information." Further consensus is needed between stakeholders of the SHIELD working group to better communicate the overall process flow of the LIVD specification and Solor's role in it.

To improve understanding of the value-added by Solor, the interviewees helped solicit and prioritize a set of additional "advanced" features that would add immediate benefit to end-users and to the business case: (1) Authoring/Editing; (2) Querying and reconciling the differences between specific versions of LIVD catalogs; (3) Representation of the LIVD data elements in the non-defining taxonomy; (4) Integration into a RESTful FHIR server.

Finally, regarding policy, regulatory, and environmental factors, the interviewees highlighted that regulators will need to make this type of highly reliable semantic representation of medical device and laboratory data a required activity. There are widely adopted standard medical terminologies used in clinical care thanks to mandates and shifts in reimbursement to reflect bundled value-based payments rather than volume-based compensation, and our interviewees commented that perhaps this could trickle down into clinical laboratories as well.

4.3 HL7 FHIR Use Case (CLIN 2005B_09.14)

To be completed as part of future deliverable.

5 CONCLUSION

To be completed as part of future deliverable.

5.1 Limitations of the Work

To be completed as part of future deliverable.

o   Small interview participant size.

5.2 Suggestions for Future Work

To be completed as part of future deliverable.

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Appendix 1: Precision Medicine Use Case Interview Guide

Introductory questions
- Can you tell me a little about yourself and your role?
- Can you tell me about the organization you work for and what it does?
- For how long have you worked with your organization?

Background with Genomic datasets
- Could you describe the level of experience you have with integrating genomic data?
- What resources do you think made working with genomics data easier/ more effective?
- Probe: What are some potential barriers that you feel present a challenge?
- Probe: What solutions have you deployed?
- Probe: Could you describe for us the successful strategies you or others have used for successful management of genomics data?

ClinVar
- To what extent have you reviewed/used ClinVar data? How familiar would you say you are?
- Does the ClinVar knowledge source used here seem like it could be useful in understanding gene variant – clinical impact?
- Are there any additional sources that could be utilized?
- Are there any sources that should not be utilized? If so, why not?

Solor demo
- What is understandable and what is confusing?
- What is ambiguous?
- Are there specific relationships (variant-gene or gene-disorder) that are easier/harder to interpret using Solor versus other data sources?
- Do you think this approach to integrating ClinVar is valid?
- Are there ClinVar data elements that we didn't use but should use?
- Are there other clinical terminology system relationships that can be used other than SNOMED CT?
- What quality assurance/control issues should be considered? (i.e., should a genomic SME perform reviews)

Ecosystem

- Overall, how do you think implementation of Solor could work for improving genomic data integration?
- Going forward, what things do you need to continue to effectively interpret genomic data relationships in Solor?
- What advice or input would you like to share with the genomics terminology community about what has worked well and what could be done differently in the interpretability of genomics data elements?
- What lessons have you learned about genomics data elements that you would want to share with others?
- What types of standards, policies, or industry changes do you think are needed to help achieve standard representations of genomics data elements?

And finally, we'd like to ask you:
- Are there any questions we did not ask that you think we should have asked?
- Do you have any questions for us? That's all the questions we have for you today. Thank you for your time and for sharing your insights on these topics.

Appendix 2: Medical Device Interoperability Use Case Interview Guide

Introductory questions
- Can you tell me a little about yourself and your role?
- Can you tell me about the organization you work for and what it does?
- For how long have you worked with your organization?

Background with Medical Devices
- Could you describe the level of experience you have with integrating laboratory/medical device data?
- What resources do you think made working with laboratory/device data easier/ more effective?
- Probe: What are some potential barriers that you feel present a challenge?
- Probe: What solutions have you deployed?
- Probe: Could you describe for us the successful strategies you or others have used for successful management of laboratory/medical device data?

Medical Devices
- To what extent have you reviewed/used laboratory/device data? How familiar would you say you are?
- Does the LIVD knowledge source used here seem like it could be useful in improve the clinical impact of laboratory/medical device data?
- Are there any additional sources that could be utilized?
- Are there any sources that should not be utilized? If so, why not?

Solor demo
- What is understandable and what is confusing?
- What is ambiguous?
- Are there specific relationships (device-specimen or specimen-analyte test) that are easier/harder to interpret using Solor versus other data sources?
- Do you think this approach to integrating LIVD is valid?
- Are there LIVD data elements that we didn't use but should use?
- Are there other clinical terminology system relationships that can be used other than LOINC/UCUM?
- What quality assurance/control issues should be considered? (i.e., should a laboratorian SME perform reviews)

Ecosystem

- Overall, how do you think implementation of Solor could work for improving laboratory/medical device data integration?
- Going forward, what things do you need to effectively use Solor for LIVD data relationships?
- What types of standards, policies, or industry changes do you think are needed to help achieve standard representations of laboratory/medical device data elements?

And finally, we'd like to ask you:
- Are there any questions we did not ask that you think we should have asked?
- Do you have any questions for us? That's all the questions we have for you today. Thank you for your time and for sharing your insights on these topics.

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Appendix 3: FHIR Use Case Interview Guide

Introductory questions
- Can you tell me a little about yourself and your role?
- Can you tell me about the organization you work for and what it does?
- For how long have you worked with your organization?

Background with FHIR
- Could you describe the level of experience you have with integrating clinical data into FHIR resources?
- What resources do you think made working with clinical terminology and FHIR more effective?
- Probe: What are some potential barriers that you feel present a challenge?
- Probe: What solutions have you deployed?
- Probe: Could you describe for us the successful strategies you or others have used for successful management of FHIR terminology content?

FHIR Terminology Services
- To what extent have you reviewed/used FHIR Terminology Services or FHIR Terminology Resources? How familiar would you say you are?
- Does the FHIR Terminology knowledge source used here seem like it could be useful in improve the clinical impact of FHIR Resources and FHIR Terminology Services?
- Are there any additional sources that could be utilized?
- Are there any sources that should not be utilized? If so, why not?

Solor demo
- What is understandable and what is confusing?
- What is ambiguous?
- Are there specific relationships (Code Systems, Value Sets, Concept Map) that are easier/harder to interpret using Solor versus other data sources?
- Do you think this approach to integrating FHIR Terminology Resources is valid?
- Are there FHIR Terminology data elements that we didn't use but should use?
- Are there other FHIR Terminology data elements that can be used other than Code System, Value Set, and Concept Map?
- What quality assurance/control issues should be considered?

Ecosystem

- Overall, how do you think implementation of Solor could work for improving FHIR Terminology Services?
- Going forward, what things do you need to effectively use Solor for FHIR Terminology Content?
- What types of standards, policies, or industry changes do you think are needed to help achieve standard representations of FHIR Terminology data elements?

And finally, we'd like to ask you:
- Are there any questions we did not ask that you think we should have asked?
- Do you have any questions for us? That's all the questions we have for you today. Thank you for your time and for sharing your insights on these topics.