Office of the National Coordinator for Health Information Technology

Sync for Genes Phase 5

STANDARDIZING GENOMIC VARIANT SHARING AND INTERPRETATION FOR CLINICAL KNOWLEDGE

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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Executive Summary

SYNC FOR GENES

The Sync for Genes program was launched in 2017 by the Office of the National Coordinator for Health Information Technology (ONC), initially in partnership with the National Institutes of Health (NIH). Sync for Genes supports ONC's aim to improve health and care through the access, exchange, and use of data, particularly by advancing the development and use of industry-supported genomic standards to standardize the sharing of genomic information among laboratories, providers, patients, and researchers. Progress has been realized through a series of phases demonstrating how technology can address the challenges of developing, implementing, and adopting genomic standards.

Aligning with ONC's vision of leveraging data for better health outcomes, the recently completed Sync for Genes Phase 5 (Phase 5) builds on earlier phases by improving data sharing and identifying opportunities to harmonize standards for more informed decision-making at the point of care. The Cures Act Final Rule solidified the use of the Fast Healthcare Interoperability Resources® (FHIR®) standard for electronic access to health information via application programming interfaces (APIs). Even prior to this milestone, Sync for Genes had leveraged the FHIR® standard, exploring how it could support the goals of this project.

Sync for Genes Phase 1 focused on pilot site testing of genomic standards in several use cases that were included in the Health Level Seven (HL7®) Clinical Genomics Work Group's Domain Analysis Model and contributed to the successful publication of the Genomics Reporting Implementation Guide (HL7® FHIR® Clinical Genomics specification) as part of FHIR® Release 3.0. Pilot sites in Sync for Genes Phase 2 expanded on the Phase 1 work by demonstrating the exchange and integration of genomic test results at the point-of-care. These sites demonstrated connectivity and exchange of clinical genomic data during an HL7® FHIR® Connectathon, using the HL7® FHIR® Clinical Genomics specification and genomic diagnostic reports. During Sync for Genes Phase 3, two demonstration projects identified gaps in the FHIR® Clinical Genomics specification when sharing and integrating genomic data generated by laboratories in the healthcare setting. Sync for Genes Phase 4 focused on sharing genomic data for patient care via APIs.

Specifically, the work conducted in Phase 5 aimed to improve access to variant annotation data to facilitate the clinical interpretation of genomic variants. A panel of experts and a demonstration site were convened to meet the goals of this phase. The panel of experts identified community needs and potential future coordinated efforts to support genomic data by developing and using data standards and knowledge bases. Children's Hospital Los Angeles (CHLA), in partnership with Elimu Informatics (Elimu), was selected to demonstrate the sharing of annotated genomic variants between clinicians and clinical genomic knowledge bases. Advances in genomic science have increased the availability of genomic data, and clinical decision support (CDS) can help increase the utilization of it for meaningful decision-making. The demonstration developed a CDS pipeline that dynamically accesses knowledge bases and presents a patient's genomic variant data to a clinician at the point of care. The CDS pipeline leveraged the draft Global Alliance for Genomics and Health (GA4GH) Variant Annotation Specification (VA-Spec) and delivered FHIR® encoded diagnostic and therapeutic implications to two proof-of-concept Substitutable Medical Apps, Reusable

Technology (SMART)-on-FHIR® apps. Additionally, opportunities were identified to continue aligning existing standards as well as enhance the usability, computability, and scalability of genomic results and information.

Phase 5 demonstrated considerable advancements in the standardization process of sharing and interpreting genomic data for clinical applications. However, challenges remain in reconciling existing standards with evolving and increasingly complex requirements. Efforts are also needed to facilitate the broader implementation and utilization of these standards within the field.

PHASE 5 PANEL KEY FINDINGS

The Phase 5 Panel confirmed the Sync for Genes Phase 4 panel findings and provided additional context. The major themes discussed included needs in the following areas: standards development, standards-based content, implementation of genomic standards, infrastructure to support genomics, use of genomic data, and training and education. Findings include:

- **Standards development**: Extend and harmonize existing standards to support new data types and use cases rather than develop new standards.
- **Standards-based content**: Improve interoperability by harmonizing genomic annotation across domains.
- **Implementation of genomic standards**: Develop or encourage an environment where implementers could evaluate standards before installation, document best practices and recommendations, and share lessons learned to lower barriers to adoption.
- **Infrastructure to support genomics**: Find and support platforms that provide guidance to institutions responsible for developing infrastructure (hardware and software) to support genomic data.
- **Use of genomic data**: Lower the barrier of use by the care team and patients by employing thoughtful CDS.
- **Training and education**: Encourage and support robust training, education, and support to enable the standardized representation, exchange, and use of genomic data and knowledge.

DEMONSTRATION PROJECT FINDINGS

The CHLA/Elimu team created a system for sharing and presenting genomic variant data. The system included a collection of genomic data that can be accessed through APIs and used by CDS applications to provide real-time recommendations to clinicians for patient care. This project demonstrated the potential for an ecosystem in which standards-based genomic knowledge is used to improve clinical care. The system used GA4GH-encoded knowledge and HL7® FHIR® Genomics Operations to annotate patient genomic data and integrate genomic findings and recommendations into electronic health records (EHRs).

Final Report

INTRODUCTION AND BACKGROUND

Sync for Genes, launched in 2017 by the Office of the National Coordinator for Health Information Technology (ONC) in partnership with the National Institutes of Health (NIH), aims to enable the sharing of standardized genomic information among laboratories, providers, patients, and researchers. The project advances the development and use of industry-supported standards, such as the Health Level Seven (HL7®) Fast Healthcare Interoperability Resources (FHIR®) standard, for consistent sharing and use of genomic data in research and clinical care by patients and their caregivers. Genomic data are critical to NIH's *All of Us Research Program* and the Precision Medicine Initiative. Together these efforts allow for a new wave of investigators to drive the future of precision medicine research. Sync for Genes builds on the knowledge gained from Sync for Science, a public-private collaboration among ONC, the Harvard Medical School Department of Biomedical Informatics, and the All of Us Research Program to develop a simplified, scalable, and secure way for individuals to access and share their electronic health record (EHR) data with researchers. Sync for Science uses and works with open FHIR application programming interfaces (API) standards that allow researchers to securely receive EHR data from third-party applications as directed by a patient.

The Sync for Genes project was designed to demonstrate incremental progress over a series of phases, with each phase building on those previously completed. This report summarizes Phases 1 through 4 and presents the work of Phase 5, including recommendations for future opportunities.

Sync for Genes Phases

Sync for Genes Phase 1: Standardizing Genomic Data

Sync for Genes Phase 1: Standardizing Genomic Data Sync for Genes Phase 1 was the first step toward integrating clinical genomic data into point-of-care. Five organizations pilot-tested use cases included in the HL7® Clinical Genomics Workgroup's Domain Analysis Model. In addition to providing a real-world test bed for standards development and proof of concept for specific use cases, Phase 1 articulated several areas for future demonstration projects and contributed to the Workgroup's FHIR® Release 3.0 of the Genomics Reporting Implementation Guide (HL7® FHIR® Clinical Genomics specification).

Sync for Genes Phase 2: Integrating Genomic Data

Sync for Genes Phase 2: Integrating Genomic Data Sync for Genes Phase 2 expanded on the work done in Phase 1 to advance the standardized sharing of genomic data using the FHIR® standard, including demonstrating the exchange of genomic test results and the integration of those results into a healthcare environment. Four organizations participated in Phase 2 and conducted demonstrations with different focus areas. Feedback from project activities was provided to the HL7® Clinical Genomics Workgroup to support the further refinement of the FHIR® Clinical Genomics specification. The pilot sites also participated in a FHIR® Connectathon, where they successfully demonstrated connectivity and exchange of clinical genomic

data using the FHIR® Clinical Genomics specification and their genomic diagnostic reports. Phase 2 also introduced the need to address industrywide challenges to meet the overall project goal. Challenges identified included variable FHIR® adoption by developers and security and data provenance gaps.

Sync for Genes Phase 3: Engaging Laboratories

Sync for Genes Phase 3 explored challenges and potential solutions to the adoption of FHIR® by laboratories that produce clinical genomic data. Two demonstration sites participated, the National Marrow Donor Program (NMDP) and the Baylor College of Medicine Human Genome Sequencing Center, building on their work as a participant in the NIH National Human Genome Research Institute (NHGRI)-sponsored Electronic Medical Records and Genomics (eMERGE) network. These demonstration sites identified gaps in the FHIR® Clinical Genomics specification as applied to laboratories. The demonstrations used the gaps identified to refine and improve the specification, which is now the candidate standard.

Sync for Genes Phase 4: Sharing Genomic Data and Information for Patient Care via APIs

Sync for Genes Phase 4 developed a set of recommendations informed by a technical expert panel (TEP) and two demonstration projects focused on developing and using APIs to share genomic information. The recommendations address the significant challenges of developing genomic standards, implementation, adoption, and use. These recommendations were designed to meet the needs of researchers, clinicians, patients, caregivers, and all other relevant health information technology industry participants. Recommendations included: 1) develop interoperable genomic standards, 2) establish a publicly accessible sandbox environment, 3) identify incentives that could positively influence the adoption of genomic standards, and 4) explore opportunities to improve the delivery of educational content in the field of genomics.

Sync for Genes Phase 5: Standardizing Genomic Variant Sharing and Interpretation for Clinical Knowledge

Sync for Genes Phase 5 (Phase 5) developed a set of strategic recommendations to help standardize genomic variant sharing and interpretation for clinical knowledge. A panel of experts and a demonstration site informed the recommendations.

The Phase 5 Panel helped prioritize future efforts that support the use of genomics by developing or leveraging data standards and knowledge bases for the clinical interpretation of genomic variants.

The demonstration site, Children's Hospital Los Angeles (CHLA), in partnership with Elimu Informatics (Elimu), demonstrated the sharing of annotated genomic information in real-time using GA4GH-encoded knowledge and delivered using HL7® FHIR® Genomics Operations. The CHLA/Elimu team showed that it is possible to establish an ecosystem that includes standards-based genomic information to help interpret patient genomic data in real-time that informs clinical decision-making (e.g., a decision about drug treatment using a patient's genomic data).

PHASE 5 PANEL

Overview

The Sync for Genes Phase 5 Panel (Phase 5 Panel) included eight participants with diverse viewpoints and backgrounds, varying areas of expertise, various roles (e.g., genomic database knowledge leaders, genomic researchers, genomic clinicians), differing areas of focus (e.g., genomic standards, exchange of genomic data), and diverse organization types (e.g., academia, health institutions). Phase 5 Panel members and their affiliated organizations are detailed in Table 1.

Table 1: Phase 5 Panel Members

Member	Organization
Melissa Cline, PhD	University of California Santa Cruz Genomics Institute
Guilherme Del Fiol, PhD	University of Utah
Mark Dunnenberger, PharmD	NorthShore University
Gail Jarvik, MD, PhD	University of Washington
Alex Mays, MD	Massachusetts General Hospital (MGH); National Cancer Institute
Sharon Plon, MD, PhD	Baylor University
Alex Wagner, PhD	Nationwide Children's Hospital
Nephi Walton, MD, MS, FACMG, FAMIA	Intermountain Healthcare Precision Genomics

Phase 5 Panel Activities

The Phase 5 Panel met to identify community needs and potential next steps to support annotating, interpreting, and contextualizing genomic variants in healthcare delivery and research. The Phase 5 Panel provided feedback to help prioritize future efforts that support the use of genomics by developing or leveraging data standards and knowledge bases for the clinical interpretation of genomic variants.

Six meetings were held between January 2022 and October 2022. Each Phase 5 Panel meeting focused on a challenge identified in Phase 4. The goal of each meeting was to validate and identify additional details and strategies to address challenges in the following areas:

- Standards development
- Standards-based content
- Implementation of genomic standards
- Infrastructure to support genomic standards
- Use of genomic data
- Training and Education

Phase 5 Panel Findings

Many challenges are associated with creating genomic-specific content harmonizing with other genomic and non-genomic standards. One of the main issues is that many of the existing genomic standards were developed with specific use cases in mind. For example, the Global Alliance for Genomics and Health (GA4GH) is research-focused, whereas Variant Call Format (VCF) specifies bioinformatics. While both are recognized standards based on their use case, sharing data between these two standards is not standardized. This perspective resulted in context-specific standards, making it difficult to use multiple standards or harmonize across existing standards. Additionally, developing formal standards is a slow process, which can result in the development of ad hoc solutions, further contributing to the problem of fragmented standards. An example of an ad hoc solution is what was completed in Phase 3 to share lab information between NMDP and the Baylor Human Genome Sequencing Center. They created custom formats that were used as a "standard" in the context of that project.

To address these challenges, it is essential to prioritize harmonizing existing standards and ensure any development of new standards is focused on interoperability, which will help create a more seamless and efficient infrastructure for using genomic information in clinical care.

The findings from the Phase 5 Panel have contributed to the proposals outlined in the “Recommendations” section of this report. These findings provide both the basis for the recommendations and the order in which to execute them, as data first needs to be in a format that can be shared and used to enable data for use in clinical decision-making.

Standards Development

Standards support integrating and using genomic data for clinical and research systems. Extending and harmonizing existing standards to support new data types and use cases is preferable to developing new standards. This will require broad community engagement and collaboration between governing entities and standards development organizations (SDOs). Specifically, GA4GH and HL7® FHIR® standards should be harmonized to improve interoperability. Policies and procedures must also be updated or developed to support standards harmonization and interoperability. Improved harmonization and coordination among standards would provide a path to implementation, lessen the barriers to adoption, enable more seamless data exchange, encourage data use, and support genomic data integration with other systems.

Standards-Based Content

"Content" includes the description of genomic variations and the annotated knowledge associated with those variations. Areas of focus for standards-based content include variant representation, vocabularies, and terminologies, all used by genomic knowledge bases to annotate alleles, genotypes, haplotypes, and phenotypes. In many cases, the description of genomic knowledge is domain or use-case-specific. Harmonization of genomic annotation across domains would improve interoperability, specifically using and reusing knowledge.

The standards used to represent genomic variations depend in part on the type and complexity of the variation, which can be classified into one of three categories:

- **Simple variants:** Methods for describing simple variants are relatively mature and robust (e.g., single nucleotide variant (SNV) substitution). The content under development for simple variants broadly represents current clinical standards.
- **Complex variants:** While efforts are underway by the community to represent complex variants (e.g., haplotypes or combinations of variations), more focus and agreement are necessary when defining terms and identifying vocabularies used to characterize complex genetic variation.
- **Structural variants:** Structural variants (e.g., copy number variation (CNV), inversions, translocations, fusions, etc.) are the most challenging to represent as standard content, as they are far more complex, and conventions for representing those variations are less mature.

Implementation of Genomic Standards

Implementing a genomic data standard involves multiple steps and a significant investment of time and resources. Before adopting a standard, producing examples is essential to understand how the data will be rendered. Additionally, prior to adoption it is helpful to set up appropriate infrastructure and access controls, and to ensure data transfer compatibility. However, this process can be challenging and expensive, especially when resources are limited. Potential adopters need access to pre-configured technical environments to lower adoption barriers eliminating the need for costly development and maintenance. Providing a sandbox environment for evaluation and feedback can help streamline the standard improvement cycle and ongoing maintenance. Implementers could benefit from an environment that allows evaluating standards, documenting best practices and recommendations, and sharing lessons learned. Such an environment would enable even those with little or no genomic knowledge to learn about standards more efficiently and lower barriers to adoption.

Infrastructure to Support Genomics

Infrastructure (hardware and software) is necessary to handle the volume and complexity of genomic data and provide supporting information and context for interpretation. This infrastructure must deliver on-demand interpretations of patient genomic data and manage the frequent changes to genomic knowledge as science advances. While infrastructure development is typically done locally by organizations that generate, capture, store, and deliver genomic data to end users, general guidance would be helpful to institutions responsible for developing infrastructure to support genomic data.

Use of Genomic Data

Using genomic information can be challenging for members of the care team and patients to understand and use. CDS can help address this challenge by providing guidance and information to help with decision-making. When planning a CDS strategy, it is essential to consider the recipient of the decision support, the type of CDS needed (such as passive linking to educational information or active interruptive alerts), the infrastructure available to support the CDS, and the metadata (such as test performed, method, sensitivity, coverage, etc.) required to support the CDS. Implementing genomic CDS can be an undertaking that exceeds the resources available at a given institution. A detailed data model and a common understanding of data semantics are needed to ensure that shared genomic data is useful, along with the ability to attach custom CDS. Currently, genomic data is shared in a non-scalable PDF format, but efforts are underway to improve standards for discrete results. The further maturation of genomic standards and their subsequent adoption by genomic knowledge bases can broadly facilitate the implementation of genomic CDS.

Training and Education

Robust training, education, and support are necessary for the standardized representation, exchange, and use of genomic data and knowledge. Examples included training materials to assist implementers, care teams, researchers, and end users in using genomic data, understanding the importance and use of standards, implementing standards effectively, and utilizing genomic data. Training and educational opportunities ensure care team members and patients have the knowledge and skills to effectively use genomic information in clinical decision-making. While activities such as an HL7® Connectathon provide opportunity for technical and implementation training, end user training is needed to ensure health care teams are able to interpret the genomic information and transfer that knowledge to the patient. Training and education are essential given the complexity of genomics and the need to accurately interpret and act upon data.

DEMONSTRATION PROJECT

Demonstration Overview

Children's Hospital Los Angeles (CHLA), in partnership with Elimu Informatics (Elimu), was selected to demonstrate dynamically annotated standardized genomic variants sharing between clinicians and clinical genomic knowledge bases. The CHLA/Elimu team established a CDS pipeline that dynamically integrates a patient's genomic variants with current knowledge. The CDS pipeline used genomic knowledge represented using the GA4GH Variation Representation and Variation Annotation specifications to deliver data to two proof-of-concept apps using HL7® FHIR®. This project aimed to improve clinicians' ability to make informed decisions about a patient's care by giving them the most up-to-date knowledge about their genomics.

Use Cases

The following use cases were selected to drive project priorities and design decisions:

- A clinician who wants to see the latest information about how a patient's genomics may affect their risk for certain types of cancer or their response to certain medications. The system should display only information that is strongly supported by evidence.
- A clinician is diagnosing a rare disease in a patient. The clinician wants to see a broader range of information about the patient's genomics, including how the patient's genomic variations may affect the function of their cells or tissues. This will help the clinician identify and prioritize potentially causative genomic variants in the diagnostic process.

Demonstration Activities

The CHLA/Elimu team enhanced the CDS pipeline to dynamically retrieve variant annotations by conducting the following activities.

HL7® FHIR® Genomics Operations is a set of rules and guidelines for using FHIR standards to exchange information about a person's genomics. The reference implementation supporting the specification can return annotated genomic data in a way that can be shared with other systems or applications. This helps facilitate the exchange of genomic information between clinicians and other healthcare providers, improving the ability to make informed decisions about a patient's care.

The CHLA/Elimu team leveraged the HL7® FHIR® Genomics Operations reference implementation GitHub repository and enhanced it to add information and context to a patient's genomic data output from three different sources: ClinVar, Clinical Interpretation of Variants in Cancer (CIViC), and Pharmacogenomics Knowledge Base (PharmGKB). ClinVar is a database of genomic variations associated with disease, CIViC is a database of information about the clinical interpretation of genomic variations in cancer, and PharmGKB is a database of how genomic variations can affect a person's response to medications. By integrating information from these three sources, the reference implementation provided clinicians with a more comprehensive understanding of a patient's genomics and how it may affect their health.

The reference implementation was also enhanced to include additional tools and resources that provide more information and context about a patient's genomic variations. SnpEff is a tool that can predict how a particular genomic variation may affect the function of a gene or protein, and SnpSift is a tool that can help filter large datasets to identify the most significant genomic variations. The gnomAD v2.1.1 database is a resource that contains a large amount of data on genomic variations from various sequencing projects. It can provide additional information on the frequency of genomic variations in different populations. By integrating these tools and resources into the reference implementation, clinicians were able to get a complete picture of how a patient's genomics may affect their health and make more informed decisions about their care. The open-source code used in this demonstration is available in the FHIR® Genomics Operations reference implementation GitHub repository.

Two proof-of-concept apps were developed to demonstrate the capabilities of the reference implementation to support clinicians in making more informed decisions about a patient's care (See Appendix A for additional details about the apps).

1. The Face Sheet app shows clinicians the latest information about how a patient's genomics may affect their health. It will only display highly curated information from the American College of Medical Genetics and Genomics (ACMG) and the field of Pharmacogenomics (PGx).
2. The Variant Summary app allows clinicians to filter and prioritize genomic variations that may be relevant to diagnosing a rare disease. This app displays all available data about a genomic variation, including diagnostic and therapeutic implications, potential effects on the function of genes and proteins, and their frequency in different populations.

HL7® FHIR® Genomics Operations Tool

The CHLA/Elimu team's system can provide clinical decision support to healthcare providers based on a patient's genomic information, helping them make informed decisions about their care and tailor treatment plans based on their unique genomic profile. They used GA4GH-encoded knowledge and HL7® FHIR® Genomics Operations to make adding and updating information about a patient's genomic variations easier. HL7® FHIR® Genomics Operations provided a consistent way for developers to access and use patient data, regardless of how it was structured internally. It also allowed for combining different data sets and ensured that variant information was consistent across sources.

HL7® FHIR® Genomics Operations is a tool still being tested and improved. The CHLA/Elimu team identified two opportunities to improve the HL7® FHIR® Genomics Operations tool:

- **Simplify the return of diagnostic and therapeutic implications:** For example, if a clinician wants to determine any molecularly guided medication treatment options for the patient, the results will show therapeutic implications (e.g., resistance or sensitivity to a medication).

- **Enable options for computing predicted molecular consequences:** An example may be if a clinician suspects a genomic variant, the results will show the presence of a variant type.

Demonstration Findings

The CHLA/Elimu team successfully demonstrated the potential for an ecosystem where genomic knowledge is standardized and can be used to inform clinical care. The system includes a repository of genomic data that can be accessed through APIs and used by CDS applications to provide real-time recommendations to clinicians at the point-of-care for a patient. Using GA4GH-encoded knowledge and the HL7® FHIR® Genomics Operations allows for managing an individual's genome and integrating genomic findings and recommendations into EHRs.

The CHLA/Elimu team's approach to dynamic annotation involved using a patient's genomic variants to provide contextually relevant information at the point-of-care. The complexity of this process may vary depending on the type of variant being annotated. For example, some variants may be more straightforward to interpret and annotate, while others may be more complex and require more in-depth analysis. By intersecting a patient's genomic variants with knowledge from standardized knowledge bases, accurate and up-to-date information was provided to clinicians to support decision-making at the point-of-care.

To further drive the industry towards an ecosystem where contextually relevant GA4GH-encoded knowledge can be delivered to clinical applications using HL7® FHIR® Genomics Operations at scale, the maturity and harmonization of the standards must be improved.

Recommendations

The following recommendations were informed by the panel and demonstration project, and are ordered by need and dependency: 1) develop, enhance, and harmonize genomic standards; 2) develop a sandbox environment for testing; 3) support the implementation and adoption (use) of genomics; and 4) enable CDS standards and capabilities.

1. Develop, Enhance, and Harmonize Genomic Standards

Although several standards are in use, they do not always work well with each other. As an example, when sharing lab information, some clinical labs use HL7® Version 2, some early FHIR adopters use HL7® FHIR®, clinicians typically use SNOMED®, and labs use Logical Observation Identifiers Names and Codes (LOINC). Currently there is no standard organization that coordinates or provides guidance regarding harmonization across multiple SDOs or standards. Any harmonization across standards used for genomics that has occurred to date has happened at a small scale addressing particular use cases. HL7® and GA4GH have both attempted to bridge that gap. However, there is much more coordination that remains to be done.

For example, a coordinated effort is needed to enhance and fill known gaps in existing standards with harmonization in mind. This will require a systematic approach focusing on priority data, terminology, and messaging standards, evaluating, harmonizing, and improving these standards. Once harmonization is underway, there must also be ongoing support to maintain alignment across standards. The improvement process will focus on providing deeper support for genomic data types, improving the computability of data, and improving semantic and syntactic alignment through harmonization. This effort will require the participation of experts in the genomics community and support from SDOs. It will also form the foundation that is needed for the other recommendations.

2. Develop a Sandbox Environment for Testing

A controlled testing environment helps implementers learn about a specification and allows them to work through challenges associated with mapping data and testing code. Developing and coordinating a collaborative environment where data harmonization teams, implementers, modelers, and end users can work together to find solutions would be beneficial. The sandbox environment can range in complexity from simple coordination of the community to more technical testing of implementations of standards. It would provide a place for the community to discuss, test, and evaluate proposed solutions and explore solutions before deciding to implement and adopt them.

Currently, much of the implementation work is done in silos, so the ideal situation would be for solutions to be developed in a more collaborative way that reflects the needs of the broader genomics community. This recommendation depends on some level of standards harmonization and will provide critical resources for the following recommendation (Support the Implementation and Adoption (Use) of Genomics).

3. Support the Implementation and Adoption (Use) of Genomics

Widespread implementation, adoption, use, and feedback are necessary for scalable interoperability, so it is essential to support the implementation and adoption of standards. By lowering barriers to adoption,

institutions will be more likely to invest in implementing infrastructure to support the use of genomic data. As adoption increases, feedback provided to SDOs will further improve the relevant specifications. This iterative, positive feedback loop will produce more robust standards and broader interoperability. Implementing genomic standards and technology is highly complex, but each implementation will require time, resources, and funding. There are several ways to support the implementation, adoption, and use of these standards and solutions, which may include the following depending on the audience:

- **Connectathons**: These are designed to be technical and collaborative sessions. These working sessions could include harmonizing standards, implementation, exchanging data, testing interoperability across harmonized standards, or utilizing data in downstream applications (e.g., CDS). This is an activity where participants can test potential solutions.
- **Training Activities**: Develop a set or create a repository of standards-related and genomics-related content to help implementers, end users, and modelers better understand how to use the proposed solutions and navigate the sandbox environment.
- **Demonstrations:** These are lunch-and-learn or brown bag sessions where users can either attend a meeting or access a demonstration on how a solution was developed, implemented, and used. Several members agreed that seeing how something was done helps to understand better what is possible and how that solution might be utilized in their environment.

4. Enable CDS Standards and Capabilities

Providing data to those who need it in a practical and actionable way can be valuable but requires a high level of interoperability between genomic knowledge bases and clinical systems (e.g., EHR). CDS can be a strategy for making genomic data actionable. It is important to note that CDS depends on implementing and adopting genomic standards and requires extensive coordination with clinical oversight groups. The process for implementing CDS is generally well-known. Several institutions already have mature genomic CDS implementations, which could inform the development and dissemination of best practices for new implementers.

Note, this recommendation depends on the input from the recommendations above. Without realizing those first, it will be difficult to enable CDS standards and capabilities.

Conclusion

Sync for Genes Phase 5 made significant progress in testing the standardization of genomic variant sharing and interpretation for clinical knowledge. By collaborating with a panel of experts and a demonstration site, Phase 5 was able to build on the progress made in earlier phases to continue to advance the program.

The CHLA/Elimu team demonstrated the sharing of dynamically annotated genomic information using GA4GH-encoded knowledge, delivered using HL7® FHIR®, which enabled access to an individual's entire genome, simplifying access to complex, voluminous, and dynamic data structures. Building on the findings from the demonstration, in collaboration with the feedback received from the Phase 5 Panel, strategic recommendations were developed to help standardize genomic variant sharing and interpretation for clinical knowledge.

While Phase 5 made considerable strides, there is still work to be done to align existing standards with current and more complex requirements, as well as to enable wider implementation and use of these standards. One way to achieve progress is by adopting standardized methods for sharing genomic data. This can enhance the usability, computability, and scalability of genomic results and information by replacing inconsistent, non-scalable formats with a common data model and standardized fields. This, in turn, would reduce the need for manual intervention and enable more advanced analysis. To this end, the recommendations presented in this report provide a roadmap for ongoing advancement. These recommendations include developing, enhancing, and harmonizing genomic standards; establishing a sandbox environment for testing; providing support for implementation, adoption, and use of genomic standards; and enabling CDS standards and capabilities to provide data to those who need it in a practical and actionable way.

Glossary of Acronyms and Terms

ACMG	American College of Medical Genetics and Genomics
API	Application Programming Interface
CDS	Clinical Decision Support
CPIC®	Clinical Pharmacogenetics Implementation Consortium
CHLA	Children's Hospital Los Angeles
CIViC	Clinical Interpretation of Variants in Cancer
CNV	Copy Number Variation
DNA	Deoxyribonucleic Acid
EHR	Electronic Health Record
eMERGE	Electronic Medical Records and Genomics
FHIR®	Fast Healthcare Interoperability Resources
GA4GH	Global Alliance for Genomics and Health
Genetics	Genetics is the study of heredity. Genetics scrutinizes the functioning and composition of a single gene.
Genomics	Genomics is the study of genes and their functions and related techniques. Genomics addresses all genes and their interrelationships to identify their combined influence on the growth and development of the organism.
HL7®	Health Level 7
LOINC	Logical Observation Identifiers Names and Codes
NHGRI	National Human Genome Research Institute

NIH	National Institutes of Health
NMDP	National Marrow Donor Program
ONC	Office of the National Coordinator for Health Information Technology
PGx	Pharmacogenomics
PharmGKB	Pharmacogenomics Knowledge Base
SDO	Standards Development Organizations
SMART	Substitutable Medical Apps, Reusable Technology
SME	Subject Matter Expert
TEP	Technical Expert Panel
Terminology	A collective term that describes the continuum of a code set, classification, and vocabulary.
VA	Variant Annotation
VA-Spec	Variant Annotation Specification
Vocabulary	A set of specialized terms that facilitates precise communication by minimizing or eliminating ambiguity (e.g., SNOMED-CT).

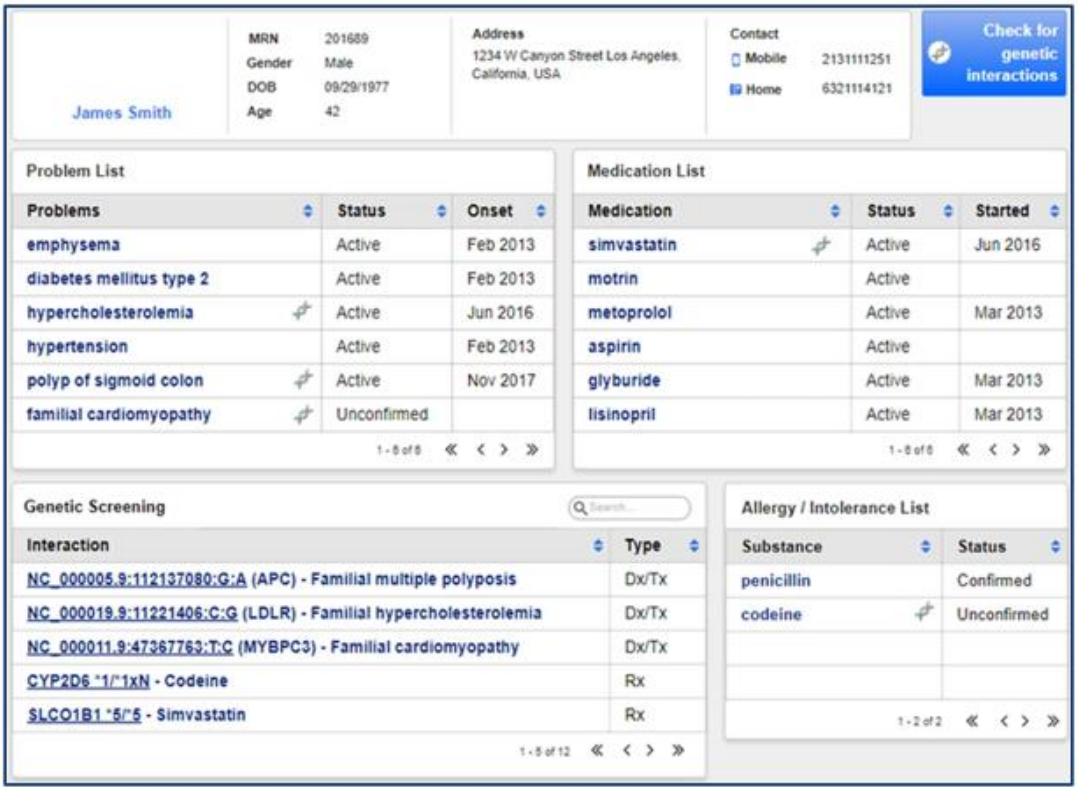
Appendix A

APPLICATIONS

Two proof-of-concept apps were developed for this project, the Face Sheet app and the Variant Summary app.

Face Sheet App

The Face Sheet app is a SMART-on-FHIR® app that shows up-to-date genomic implications.

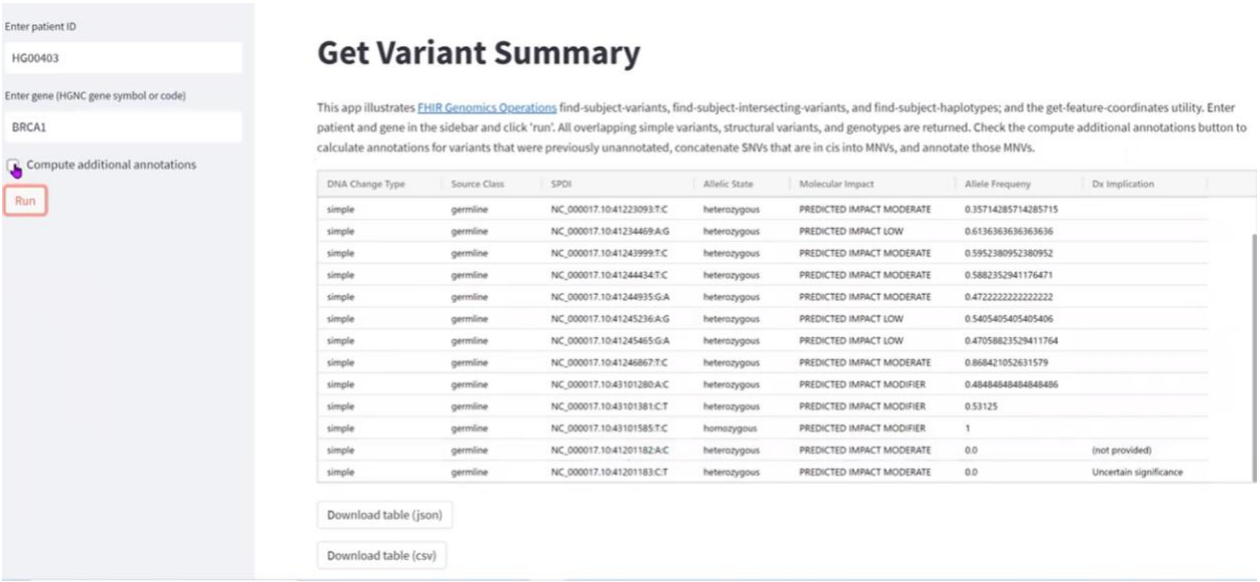


Genomic interactions are displayed in four widgets, as detailed below:

Widget	Description
Genetic Screening	This widget shows full ACMG and Clinical Pharmacogenetics Implementation Consortium (CPIC®) Level A screening results. Clicking on a given interaction surfaces a dialog box with additional details.
Problem List	Where a variant detected through genetic screening is a potential etiology of an item on the patient's problem list, that problem list item is flagged. Clicking a DNA icon surfaces a dialog box with additional details.

Widget	Description
Medication List	Where a variant detected through genetic screening potentially affects the behavior of a patient's medication, that medication is flagged. Clicking a DNA icon surfaces a dialog box with additional details.
Allergy / Intolerance List	Where a variant detected through genetic screening is a potential basis for an identified allergic reaction, that allergy is flagged. Selecting a flagged item surfaces additional details about the possible genomic interaction. Selecting a DNA icon emerges a dialog box with further information.

Variant Summary App



The Variant Summary app is an open-source app that broadly summarizes implications and consequences for variants in specified regions of a patient's genome. The intent is to enable filtering and prioritization of variants for rare disease discovery; this was done by following the methods developed by the working group formed through the Medical Genome Initiative.