



The Office of the National Coordinator for
Health Information Technology

Sync for Genes Phase 3

ENGAGING LABORATORIES FINAL REPORT

Prepared by Audacious Inquiry on behalf of the Office of the
National Coordinator for Health Information Technology under
Contract No. HHSM-500-2017-000101
Task Order No. HHSP23320100013U

January 2021



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Acknowledgement

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Executive Summary

INTRODUCTION

Under the direction of the Office of the National Coordinator for Health Information Technology (ONC), in collaboration with the National Institutes for Health (NIH), Sync for Genes Phase 3 continued the overall goal of the Sync for Genes project by further exploring approaches of exchanging and integrating genomic data into healthcare systems. Sync for Genes Phases 1 and 2 demonstrated the need for additional work on the Health Level Seven (HL7®) Fast Healthcare Interoperability Resources (FHIR®) Genomics Reporting Implementation Guide (IG) standard for trial use (STU) and the positive impact that carefully crafted pilot activities can have on the development of standards. Previous Sync for Genes phases highlighted the importance of incorporating testing laboratories (labs) in the development of standards. Testing labs are the primary producers of FHIR-formatted data and an essential participant in the exchange of clinical genomic results. Sync for Genes Phase 3 explored the potential use of the HL7 FHIR Genomics Reporting IG (STU1) for sharing genomic data generated by testing labs. Through demonstration projects, challenges and solutions were identified through the implementation of the HL7 FHIR Genomics Reporting IG (STU1). Sync for Genes Phase 3 took a collaborative approach to clinical genomics standards development by aligning with leading industry efforts to identify high-impact enhancements to the HL7 FHIR Genomics Reporting IG (STU1) that will support current and future genomic testing requirements and facilitate broad adoption.

DEMONSTRATION PROJECTS

Two demonstration projects were selected for Sync for Genes Phase 3 that informed the HL7 FHIR Genomics Reporting IG (STU1).

- The Baylor College of Medicine Human Genome Sequencing Center (BCM-HGSC) participated as a genomic testing lab, building upon the work done as a participant in the NIH National Human Genome Research Institute (NHGRI)-sponsored Electronic Medical Records and Genomics (eMERGE) Network. The BCM-HGSC demonstration project conducted the following:
 - Implemented an eMERGE FHIR Specification;
 - Generated clinical reports in FHIR format;
 - Evaluated the utility of the current version of the HL7 FHIR Genomics Reporting IG (STU1) for use in a clinical research network setting; and
 - Explored high-impact enhancements to the HL7 FHIR Genomics Reporting IG (STU1) that would support current and future genomic testing requirements and shared findings with the HL7 Clinical Genomics Work Group.
- The National Marrow Donor Program (NMDP), part of a national program supporting transplants, participated in Sync for Genes Phase 3 by performing the following activities:
 - Partnered with a histocompatibility typing lab to develop a translator tool to convert human leukocyte antigens (HLA) report data generated by the lab into FHIR format; and
 - Leveraged the HL7 FHIR Genomics Reporting IG (STU1) and constrained it to create an HLA Reporting IG and shared lessons learned with the HL7 Clinical Genomics Work Group.





FINDINGS AND LESSONS LEARNED

The Sync for Genes Phase 3 demonstration projects leveraged established relationships between data senders and receivers, enabling the demonstration projects to proceed more efficiently and deeply than might otherwise have been possible. Both demonstration projects created customized IGs based on the HL7 FHIR Genomics Reporting IG (STU1) for their respective highly specialized use cases. The BCM-HGSC demonstration project created the eMERGE FHIR Specification, which established a standardized way to represent clinical genetic test results for sharing across networks. The NMDP demonstration project developed the HLA Reporting IG and a translator tool to convert HLA report data into FHIR format. The NMDP project efforts enable better representation of HLA data in FHIR and the exchange of this data in a standardized format.

Both demonstration projects identified challenges and solutions when working with the HL7 FHIR Genomics Reporting IG (STU1) that were communicated to the HL7 Clinical Genomics Work Group for future consideration. Leveraging established relationships and working collaboratively with the HL7 Clinical Genomics Work Group allowed the demonstration projects to be efficient and effective. This approach is recommended to continue to make progress with improved access to standardized genomics data at the point-of-care and for research to realize the goals of precision medicine. The Sync for Genes project continues to pave the way for efficient interoperable use of genomic data to inform clinical decision-making and research.





Introduction and Background

Genomic data have emerged as an important informant in precision medicine and relevant research aimed at tailored treatment and prevention strategies based on people's unique characteristics, including environment, lifestyle, and biology. Access to standardized genomic data at the point-of-care will enable the use of the entire genome of a patient to diagnose diseases and adjust medications exclusively for that patient.¹ Clinical genomics uses a patient's genomic profile to diagnose or assess risk of disease and tailor treatment strategies, such as medications.² This rapidly evolving field requires complex data to support clinical genomics and precision medicine research. For genomic data to be used efficiently to inform clinical decision-making, genomic data need to be interoperable (i.e., shared in a consistent, computable way that is semantically robust) and adaptable as medical science and clinical practice evolve.³

SYNC FOR GENES

To advance clinical genomic data collection, sharing, and availability across electronic health records (EHRs), ONC launched the Sync for Genes project in 2016, in partnership with NIH.⁴ As a flagship project under the Precision Medicine Initiative (PMI),⁵ Sync for Genes has paved the way for patients to share genomic information with researchers to support clinical genomics and precision medicine research. It has undergone three phases of development.

Sync for Genes Phase 1 focused on the standardization of genomic data exchange by leveraging HL7 FHIR to test and validate new HL7 specifications for clinical genomics.⁶ This phase of the project laid the foundation for the development of HL7 FHIR artifacts to support genomics data exchange within healthcare systems. Sync for Genes Phase 1 captured specific FHIR technical implementations through the coordination of five demonstration sites, each with their own specific use cases. All five organizations were successful in leveraging HL7 FHIR to address their use cases and contributed to the HL7 Clinical Genomics Work Group's Domain Analysis Model (DAM).^{7,8} Pilots created/tested FHIR genomics implementations for conformance and throughout the pilot period and provided feedback on specific issues seen. The DAM was intended to be used as the basis for the development and execution of Sync for Genes. The DAM outlines multiple scenarios centered on sequencing in clinical and translational settings where FHIR genomics can be applied and served as a foundational guide for the five demonstration sites.

Sync for Genes Phase 2 began in 2018 and leveraged lessons learned from Sync for Genes Phase 1 by exploring ways to bring clinical genomic data to the point-of-care and make it available for research.^{9,10} Four organizations participated in Sync for Genes Phase 2 as demonstration sites. Each site tested the HL7 FHIR Genomics Reporting IG (STU1), which was under development by the HL7 Clinical Genomics Work Group.^{11,12} Each site applied the implementation guide under development to their unique use cases and workflows and shared feedback with the HL7 Clinical Genomics Work Group throughout the process. Sync for Genes Phase 2 demonstrated the benefit of active collaboration between the demonstration sites and the HL7 Clinical Genomics Work Group. This collaboration helped to identify missing or misaligned semantics in the implementation guide and areas that needed further modification. Sync for Genes Phase 2 highlighted the need to test diverse use cases in the standard development process to ensure the effective integration of genomic data. Sync for Genes Phases 1 and 2 demonstrated the need for additional guidance and testing of the HL7 FHIR Genomics Reporting IG (STU1). These phases highlighted the importance of including testing labs during the development and testing process, as they are the primary producers of FHIR-formatted data and essential to the exchange of clinical genomic results.

The application of genomic data to inform an individual's healthcare is an ambitious goal that requires the seamless exchange of complex data between a variety of partners, including lab and healthcare provider organizations. The advancement of personalized medicine and initiatives such as the *All of Us* Research Program continue to be supported by activities such as these, which inform and further develop the standards that enable data sharing, facilitate research, and pave the way to improving patient care.





Sync for Genes Phase 3: Engaging Laboratories



OVERVIEW

Launched in 2019, Sync for Genes Phase 3 explored the use of the HL7 FHIR Genomics Reporting IG (STU1) to report genomic data generated by testing labs. The goal was to identify challenges that testing labs experience when adopting health IT standards. Solutions were also identified to facilitate broad adoption of standards by generators of genomic data. Lessons learned from the demonstration project sites informed needs for the further development of the HL7 FHIR Genomics Reporting IG (STU1).

DEMONSTRATION PROJECT TESTING APPROACH

Demonstration project testing is necessary to develop and advance a standard. Sync for Genes Phase 3 focused on identifying HL7 FHIR Genomics Reporting IG (STU1) gaps and ambiguities that could potentially hinder the accurate rendering or exchange of clinical genomic test results. To maximize the opportunity to collect feedback, demonstration project activities were designed to engage partner organizations representing both labs that generate clinical genomic data and users who order tests and receive results. This approach leveraged established relationships between data senders and receivers and enabled demonstration project work to proceed more efficiently and deeply than might otherwise have been possible.

Participating organizations represented different use cases, types of genomic testing, and implementation environments. In addition, the demonstration projects had the following characteristics:

- **Established partnerships**, a pair of sites that **represented** the generation (sender) and consumption (receiver) of genomic data;
- A clinical or scientifically motivated use case that **illustrated** a unique challenge in the exchange of genomic data;
- **Engaged in** activities related to FHIR implementation;
- In-house technical teams **with** intermediate knowledge of FHIR tooling and technology;
- **Actively participated** in the FHIR development and/or adoption community;
- Committed to the early adoption of the HL7 FHIR Genomics Reporting IG (STU1);
- **Contributed** to genomics standards development activities; **and**
- Strategic business priorities that **aligned** with Sync for Genes program goals, allowing an opportunity to leverage internal site efforts and resources.

Sync for Genes Phase 3 demonstration projects each had different use cases, technological environments, and data sources, which allowed for the ability to test and inform different aspects of the HL7 FHIR Genomics Reporting IG (STU1).





BAYLOR COLLEGE OF MEDICINE HUMAN GENOME SEQUENCING CENTER

Baylor College of Medicine Human Genome Sequencing Center (BCM-HGSC) is committed to improving healthcare through genomic testing at its HGSC clinical lab, a molecular diagnostic lab operating within BCM-HGSC.¹³ The lab provides testing services for both diagnostic clinical testing and research. The goal of this demonstration project was to further evaluate the HL7 FHIR Genomics Reporting IG (STU1) for use in a research network setting where clinical genomic results are produced.

Background

The translation of discoveries in human genetics into clinical practice has motivated the development of robust methods for exchanging clinical genomic data. One method funded by NIH NHGRI is the eMERGE Network, which is now entering its fourth phase. The primary goal of the eMERGE Network is to develop, disseminate, and apply approaches to research that combine biorepositories with EHR systems for genomic discovery and genomic medicine implementation research.¹⁴ The previous phase of the eMERGE Network included two clinical sequencing and genotyping labs, BCM-HGSC and the Broad Institute, which generated data for research sites participating in the network. These two clinical sequencing and genotyping labs served as centralized resources that returned results to participating sites. The participating sites then integrated the genetic data into EHR systems and used the results for research studies.

eMERGE Network participants identified a need for a standardized format to represent clinical genetic test results that could be seamlessly shared across disparate EHR systems facilitating cross-network data sharing. Previously, *ad hoc* homegrown solutions had been created to share this information, but those solutions were not suitable and would not scale for use across the eMERGE Network. The eMERGE Network sought to develop a less fragile, more robust solution for data exchange; therefore, the HL7 FHIR Genomics Reporting IG (STU1) was chosen for evaluation.

BCM-HGSC and the Broad Institute, the two eMERGE Network clinical sequencing and genotyping labs, worked collaboratively with the HL7 Clinical Genomics Work Group to create a FHIR specification that was based on the HL7 FHIR Genomics Reporting IG (STU1) and tailored to the needs of the eMERGE Network.¹⁵ Both clinical sequencing and genotyping labs used this customized specification to demonstrate that reports could be generated in a common format. Two eMERGE Network participating sites, Northwestern University and Johns Hopkins University, received the reports and evaluated their use for clinical decision support.

The eMERGE Network was selected as a Sync for Genes Phase 3 demonstration site for several reasons:

- The research network was well established and data sharing agreements between the participating sites were already in place;
- Real clinical genomic results were readily available for testing and electronic infrastructure was in place at each site to support sending and receiving results;
- All participants were familiar with FHIR and were committed to its early adoption and evaluation; and
- The eMERGE Network contained two different clinical sequencing and genotyping labs producing data and two different sites consuming data, therefore, four different stakeholder organizations could be engaged in a single demonstration project.

Partnership with the eMERGE Network was synergistic, making BCM-HGSC an ideal demonstration project for Sync for Genes Phase 3.





Description of Demonstration Project Activities

As a Sync for Genes Phase 3 demonstration project, BCM-HGSC expanded the eMERGE Network activities and conducted the following:

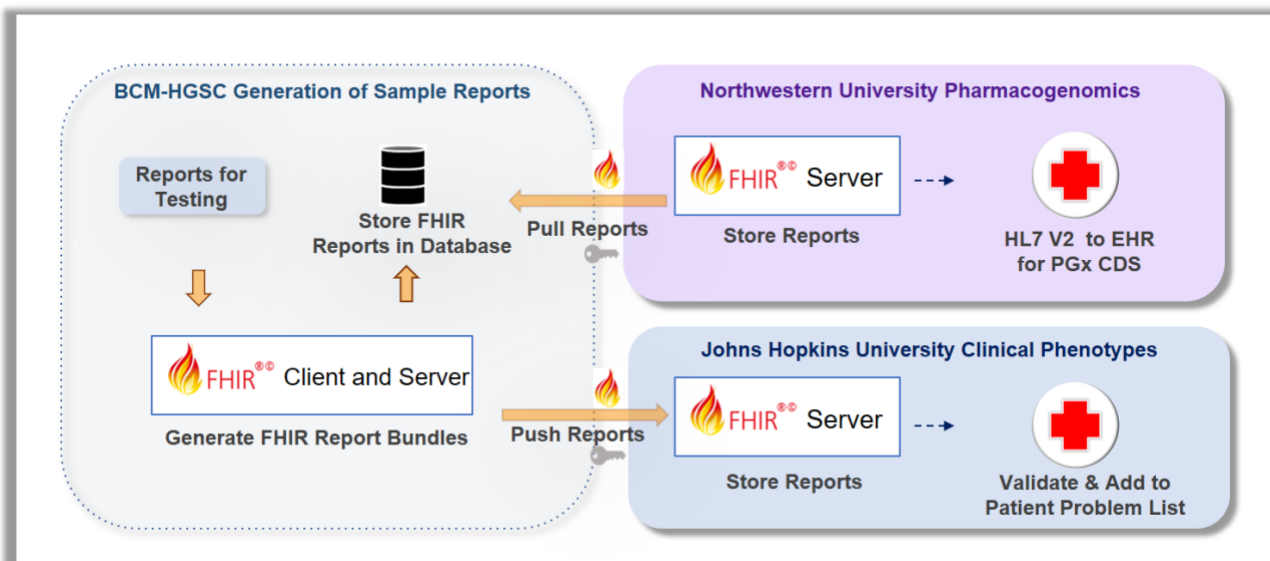
- Completed the design of the eMERGE FHIR Specification;
- Implemented the HL7 FHIR Genomics Reporting IG (STU1) and generated clinical reports in FHIR format;
- Evaluated the utility of the current version of the HL7 FHIR Genomics Reporting IG (STU1) for use in a clinical research network setting; and
- Explored high-impact enhancements to the HL7 FHIR Genomics Reporting IG (STU1) that would support current and future genomic testing requirements.

The eMERGE FHIR Specification was created based on the HL7 FHIR Genomics Reporting IG (STU1).¹⁶ Throughout the implementation process, changes needed were uncovered and resolved to formulate the eMERGE FHIR Specification. As changes were identified, they were shared with the Clinical Genomics Work Group for future updates to the HL7 FHIR Genomics Reporting IG (STU1).

The BCM-HGSC demonstration project also aimed to streamline adoption for diagnostics labs using the HL7 FHIR Genomics Reporting IG (STU1) to represent clinical genomic results, and then transmit the results in FHIR format to client systems that use the data.

The figure below illustrates the flow of test data between the sites that participated in the demonstration project. Clinical genomic reports were exchanged between FHIR servers at each organization. The reports then were stored in EHR systems at Northwestern University for pharmacogenomics and Johns Hopkins University for clinical phenotypes, as detailed below in the diagram.

Figure 1: Baylor College of Medicine Human Genome Sequencing Center Demonstration Project





Summary of Key Findings and Outcomes

The demonstration project activities performed by BCM-HGSC included the final development of an implementation guide that was based on the HL7 FHIR Genomics Reporting IG (STU1) and customized to support the eMERGE Network needs. The eMERGE FHIR specification was successfully implemented and used to generate 194 eMERGE Clinical Genomic Reports, which were exchanged with Northwestern University and Johns Hopkins University.

Collaboration with the HL7 Clinical Genomics Work Group helped the demonstration project identify solutions for grouping results from multiple panel tests together into a single report and identified how secondary genomic findings could be distinguished from primary findings within the report. The BCM-HGSC demonstration project identified a method to capture technical details about the methodology used for testing and a way to incorporate recommendations that could help clinicians use the test results to inform clinical decision-making.

The BCM-HGSC demonstration project activities identified several areas of the HL7 FHIR Genomics Reporting IG (STU1) that need further development, such as a way to include comments pertaining to the report itself and interpretations within the report as opposed to comments about the test results. Other areas for future work include developing methods for specifying the genomic region(s) covered by the test and capturing more detailed information about the genomic variants that were detected. This additional development work was submitted to the HL7 Clinical Genomics Work Group for future consideration.

NATIONAL MARROW DONOR PROGRAM

The National Marrow Donor Program (NMDP) is a national nonprofit organization that operates Be The Match, a program dedicated to helping patients get life-saving transplants. NMDP is focused on developing standards that ensure donors and patients receive high-quality care while meeting government standards.¹⁷ This includes collaborating with testing labs to generate genomic data used to match donors and recipients and ensure that genomic data can be transmitted accurately to ensure patient safety and match efficiency. This pilot project's goal was to describe how to report HLA genotyping results built off of the HL7 FHIR Genomics Reporting IG (STU1).¹⁸

Background

Successful tissue transplantation requires a close match between the donor's genomic profile and the recipient's genomic profile, a process called histocompatibility typing. Histocompatibility typing for stem cell and organ transplant is complex and is defined by the makeup of an individual's HLA genes, or HLA genotype. Thousands of HLA alleles (different forms of the genes) are known, and new alleles are discovered frequently, which complicates the reporting and interpretation of HLA test results.¹⁹ The HLA region of the genome is also technically challenging to test accurately. These factors, combined with the clinical importance of matching, require genomic test results be represented precisely. As a result, histocompatibility test results are reported using a highly specialized format called the Histoimmunogenetics Markup Language (HML), a community-developed standard and potential general-purpose format for exchanging genetic typing data.²⁰

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research collaborative between NMDP/Be The Match and the Medical College of Wisconsin.²¹ While NMDP focuses on matching patients with donors and facilitating the transplant, CIBMTR focuses on post-transplant outcomes research. In Phases 1 and 2 of Sync for Genes, NMDP/CIBMTR developed and implemented a tool to convert HLA genotyping reports rendered in HML format to HL7 FHIR. This conversion enabled partner transplant centers to send HLA reports using HL7 FHIR, which is widely supported by clinical systems including EHRs. This set the foundation for NMDP to develop local infrastructure to consume HL7 FHIR data from the HLA testing lab.

The NMDP/CIBMTR was selected as a Sync for Genes Phase 3 participant because it represented an opportunity to further evaluate and extend the HL7 FHIR Genomics Reporting IG (STU1) to support the HLA use case that is currently only partially supported by the HL7 FHIR Genomics Reporting IG (STU1). Additionally, NMDP/CIBMTR led the development of the HML standard, was committed to the adoption of





FHIR technology, and was an active participant in the HL7 FHIR community. Finally, NMDP/CIBMTR had pre-existing partnerships with histocompatibility testing labs and was working with them to implement and test FHIR-based methods for exchanging HLA test results.

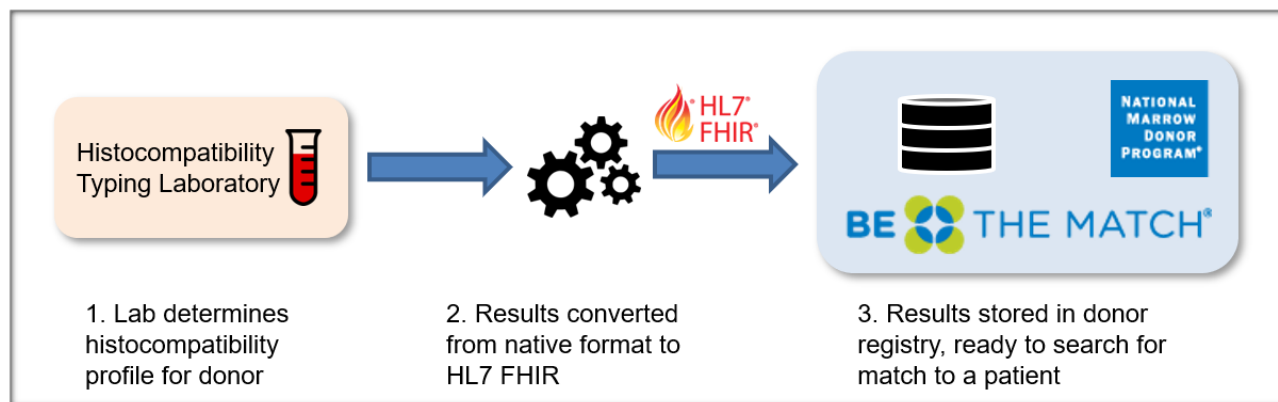
Description of Demonstration Project Activities

NMDP/CIBMTR previously led the development of an HLA-specific profile of the HL7 FHIR Genomics Reporting IG (STU1). As a Sync for Genes Phase 3 demonstration site, NMDP/CIBMTR leveraged the HL7 FHIR Genomics Reporting IG (STU1) and constrained it to create the HLA Reporting Implementation Guide²². The HLA Reporting IG included local extensions that were necessary to support the requirements of the highly specialized HLA use case and incorporated specialized rules that were unique to histocompatibility typing. The HLA Reporting IG was created to overcome the challenges of using the HL7 FHIR Genomics Reporting IG (STU1) to represent HLA results.

In addition to developing the HLA Reporting IG, NMDP/CIBMTR leveraged a relationship with Versiti, a lab that provides 11 percent of all clinical HLA typing reports in the United States. Together, NMDP/CIBMTR and Versiti implemented and tested a translator tool that enabled HLA test results to be reported in FHIR format.²³ The translator tool enabled the production and exchange of FHIR-formatted HLA genotype reports that contained molecular sequences, which was not supported by the HL7 FHIR Genomics Reporting IG (STU1). The translator tool eliminated the need to exchange HLA data using HML as an intermediate format.

The figure below illustrates the flow of test data between the lab and NMDP using the custom translator tool to convert to a FHIR format.

Figure 2. National Marrow Donor Program Pilot





Summary of Key Findings and Outcomes

The NMDP demonstration project activities included the development of a new HLA Reporting IG and a translator tool to convert HLA report data into FHIR format. As a result of this demonstration project, HLA data can be better represented in FHIR and exchanged in a standardized format.

A key barrier that the NMDP demonstration project addressed was the difficulty for a genetic testing lab to invest the resources required to upgrade existing software to support the FHIR standard, especially when that standard is still under active development. The development of the translator tool allowed the lab to explore and evaluate the FHIR standard's ability to render test reports without requiring a large investment of resources or a software system's upgrade/reconfiguration. This approach may encourage early adopters to implement FHIR because it only requires developing a translator that converts existing output to FHIR format. This solution enabled the ability to test the specification and provide feedback to the FHIR development teams without incurring significant cost or a disruption to production.

The NMDP demonstration project showed an increase in efficiency and more accurate data representation by translating results directly into FHIR format rather than performing the multiple, sequential translations required if existing formats were used. The use of intermediate formats, such as HML, could result in data loss and/or the introduction of ambiguities that require the message recipient to make assumptions when interpreting the data. The HLA Reporting IG created captured test results more robustly and eliminated the need for multiple translation steps between formats.

Additionally, the NMDP demonstration project identified several opportunities for further development of the HL7 FHIR Genomics Reporting IG (STU1). This work identified the need for additional support to capture information about organizations that act on behalf of other organizations. This is common in transplantation scenarios where one organization may report results on behalf of another organization. The NMDP demonstration project also identified the need to develop methods that better capture novel genomic results and parameters that support organization-specific workflows.





Findings and Lessons Learned

FEEDBACK TO ADVANCE THE FHIR CLINICAL GENOMICS STANDARD

Sync for Genes Phase 3 supported the advancement of the HL7 FHIR Genomics Reporting IG (STU1) specification by providing feedback derived from demonstration projects to the HL7 Clinical Genomics Work Group. The mechanisms used to provide this feedback included participation in the HL7 Clinical Genomics Work Group meetings and the use of HL7 message boards and messaging tools.

SUMMARY OF FINDINGS AND LESSONS LEARNED

The demonstration projects represented early adopters of the HL7 FHIR Genomics Reporting IG (STU1), which was still emerging. During the demonstration project activities, several challenges were encountered; although some of those challenges were specific to a particular scenario, most were more broadly applicable. The findings and the lessons learned from the Sync for Genes Phase 3 demonstration project activities are summarized below.

Semantic Representation

Much of the ambiguity that is encountered when data are exchanged is a result of different interpretations of the same data elements. This ambiguity can result from 1) a lack of clarity in labels and definitions; or 2) relationships between structural elements. Additionally, extensions to, or customizations of, a specification may be needed to support specialized requirements, as demonstrated by the participants in Phase 3; yet those modifications can be misinterpreted by the recipient of the data. To achieve robust interoperability and maximize data reuse, specifications must be developed based on a stable and well-designed semantic model. Such a model to support the clinical genomics domain is under development by the HL7 Clinical Genomics Work Group, but it is still nascent and requires further expansion to better support the complex use cases exemplified by Sync for Genes Phase 3 activities.

Complex Genomic Reports

As the scale of clinical genomic testing increases, more data can be generated at a lower cost. It is common for a genetic test to include a panel of tens or even hundreds of genes. The data resulting from a panel test must be organized to enhance readability and clinical utility. For example, genetic results often are grouped by clinical indication (i.e., reason for ordering the test), subdomain (e.g., pharmacogenomics, histocompatibility profile), or risk of developing a disease (e.g., cardiac disorders). The test reports that were rendered in FHIR by the participants in Sync for Genes Phase 3 contained complex structures of sections and subsections that were difficult to represent in FHIR. As a result, the demonstration project sites identified the need for additional standards development activities before FHIR can accurately reflect the complex structure of specialized reports.

Unsupported Data Types

The accurate interpretation of genomic data requires a nuanced understanding of many factors that can influence the use and characteristics of this data in a particular context. Although more types of data have been supported as FHIR has matured, the demonstration project activities in Sync for Genes Phase 3 identified many types of data that were not well supported. Some examples include information about workflow or clinical context, inter-organizational relationships, comments, and metadata that are not fully represented in the FHIR specifications. Additionally, detailed data elements such as precise definitions of genetic variants, the genomic regions covered by a given assay, the expression of novel results unique to a patient, and the actual genomic sequence were difficult to represent. As the demonstration projects exhibited, to support these data types, the FHIR specification needs to be further enhanced.





Generalization vs. Customization

The FHIR standard is based on a small number of resources, which represent generalized, common structures for different data types. These resources are constrained into profiles and combined into HL7 FHIR Genomics Reporting IG (STU1) for use within specialized contexts. The HL7 FHIR Genomics Reporting IG (STU1) was used as a starting point for both demonstration projects in Phase 3, adding additional IG enhancements to accommodate the specific needs of each demonstration project. An advantage of this approach is the ability to generate specifications that are tailored to a particular set of requirements. This can be a disadvantage as it introduces another barrier to interoperability, as a recipient of a highly specialized message must support its corresponding profile or IG to ensure the data is preserved accurately. Therefore, it is important to find a balance between generalization and customization and reflect that balance within the HL7 FHIR Genomics Reporting IG (STU1).

Translators Tools

A significant barrier to the early adoption and testing of an emerging standard is the cost (e.g., time, money, and personnel) required to implement the standard and integrate it into an existing system. The participating organizations in Sync for Genes Phase 3 mitigated those costs by implementing their respective FHIR solutions in parallel to existing environments. The demonstration projects were able to test the specification and provide feedback without incurring the cost or disruption necessary to implement in production. It is advantageous to encourage the early adoption and testing of standards through the development and use of translator tools. Translator tools transform content from a native format to and from FHIR. This approach enables more efficient adoption of a standard, as users don't have to wait for software developers to upgrade systems to support standards.

POSSIBLE FUTURE DIRECTIONS

Sync for Genes Phase 3 engaged demonstration projects that leveraged existing partnerships, which allowed the demonstration projects to achieve outcomes more quickly and conduct more thorough testing. This approach was highly effective, produced significant results, and is recommended to continue this work effectively and efficiently. As the application of genomics in medicine grows, there will be an increasing need to exchange even more specialized data, including highly granular primary data (e.g., complex genomic variations, arbitrary layers of interpretations, and metadata at all levels). The structure of genetic testing reports needs additional improvement to increase readability and clinical decision-making; therefore, standards need to be enhanced to support genomic data for additional complex data types (e.g., to support risk prevention and diagnosis). To maintain interoperability, even as the data becomes more complex and specialized, more work is needed to establish shared meaning across complex genomic variations and to guide future standards development.





Conclusion

The activities conducted during Sync for Genes Phase 3 resulted in significant advancements in the development and use of FHIR for the exchange of clinical genomic data, which are necessary to support the goals of PMI. The participating organizations successfully completed demonstration projects that included the implementation and testing of specialized FHIR IGs (i.e., eMERGE FHIR Specification, HLA Reporting IG) that were built upon the HL7 FHIR Genomics Reporting IG (STU1). The eMERGE FHIR Specification enabled cross-network sharing of clinical genetic test results, and the HLA Reporting IG enabled reporting of HLA genotyping results.

The outcomes from the project activities included specific feedback to the FHIR development teams and, in many cases, solutions to challenges that were identified during implementation and testing. Those outcomes will help inform future development of the standard, and the lessons learned through these pilot projects can serve as a roadmap for other organizations that are interested in implementing FHIR for genomic medicine.





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Appendix A: Glossary of Acronyms

Acronym	Definition
BCM	Baylor College of Medicine
CIBMTR	Center for International Blood and Marrow Transplant Research
EHR	Electronic Health Record
eMERGE	Electronic Medical Records and Genomics
FHIR	Fast Healthcare Interoperability Resources
HGSC	Human Genome Sequencing Center
HL7	Health Level Seven International
HLA	Human Leukocyte Antigens
HML	Histoimmunogenetics Markup Language
NIH	National Institutes of Health
NHGRI	National Human Genome Research Institute
NMDP	National Marrow Donor Program
ONC	Office of the National Coordinator for Health Information Technology
PMI	Precision Medicine Initiative





Appendix B: Glossary of Terms

Term	Definition
Electronic Medical Records and Genomics (eMERGE) Network https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE	National Institutes of Health (NIH)-organized and funded consortium of U.S. medical research institutions. The Network brings together researchers with a wide range of expertise in genomics, statistics, ethics, informatics, and clinical medicine from leading medical research institutions across the country to conduct research in genomics, including discovery, clinical implementation, and public resources. eMERGE was announced in September 2007 and began its third phase in September 2015.
eMERGE FHIR Specification https://emerge-fhir-spec.readthedocs.io/en/latest/issuess_and_resolutions.html	Built on the HL7 FHIR Genomics Reporting Implementation Guide (STU1). Details the issues identified and resolved for eMERGE specific needs.
Fast Healthcare Interoperability Resources (FHIR) https://www.hl7.org/fhir/overview.html	An HL7 standard for exchanging healthcare information electronically. FHIR aims to simplify implementation without sacrificing information integrity. It leverages existing logical and theoretical models to provide a consistent, easy-to-implement, and rigorous mechanism for exchanging data between healthcare applications.
HLA Reporting Implementation Guide http://fhir.b12x.org/ig/hla-reporting/	Human leukocyte antigen genotyping is fundamental for research and clinical practice in immunogenetics and histocompatibility. This HLA Reporting Implementation Guide (IG) describes how to report HLA genotyping results using HL7 FHIR. It relies heavily on the HL7 FHIR Genomics Reporting Implementation Guide (STU1) developed by the HL7 Clinical Genomics Work Group, constraining profiles for Genetics Report, <u>Genotype</u> and <u>Haplotype</u> . It also constrains the Molecular Sequence resource to allow reporting sequencing results together with novel variants.
HL7 FHIR Genomics Reporting Implementation Guide (STU1) http://hl7.org/fhir/uv/genomics-reporting/STU1/	Genomics involves complex data structures. Sharing this information in a way that is consistent, computable and that can accommodate the ongoing evolution of medical science and practice can be valuable. There is value in the ability to easily sort, filter, and perform decision support on such information, which results in care improvements. The HL7 FHIR Genomics Reporting Implementation Guide is transmission protocol-independent, the data structures could be used in RESTful, messaging, document or other paradigms. Currently, the IG focuses solely on data structures (e.g., what data should be/might be present, and how it should be organized). It does not address workflows around how reports are requested, created, approved, routed, delivered, amended, etc. The IG is not fully complete--portions of the implementation guide are provided for "framework purposes only."
Health Level Seven International (HL7) https://www.hl7.org/about/index.cfm?ref=nav	Founded in 1987, Health Level Seven International (HL7) is a not-for-profit, ANSI-accredited standards developing organization dedicated to providing a comprehensive framework and related standards for the exchange, integration, sharing, and retrieval of electronic health information that supports clinical practice and the management, delivery, and evaluation of health services. "Level Seven" refers to the seventh level of the International Organization for Standardization (ISO) seven-layer communications model for Open Systems Interconnection (OSI)—the application level. The application level interfaces directly to and performs common application services for the application processes.





Term	Definition
Health Level Seven International (HL7) Clinical Genomics Work Group https://confluence.hl7.org/display/CGW	The Clinical Genomics Work Group supports the HL7 mission to create and promote its standards by enabling the semantically meaningful exchange of data between parties interested in clinical, personal, and population genomic information and family health history, which are required to support personalized/precision medicine. The focus of the clinical genomics domain is the identification of an individual’s genomic data and family health history, to better understand the underlying genetic factors contributing to disease and health, and the linking to relevant clinical information including both data and knowledge.
HL7 Clinical Genomics Work Group’s Domain Analysis Model (DAM) http://www.hl7.org/Special/committees/clingenomics/products.cfm	The HL7 Domain Analysis Model: Clinical Genomics features use cases key to personalized genomic medicine and translational research, including more typical scenarios for testing of a person’s inherited or germline genome, cancer genomics/tumor profiling, early childhood developmental delay, neonatal testing, and newborn screening. The focus is on use cases that can be found in practice at some locations clinically today.
HLA Genotyping https://bethematch.org/transplant-basics/matching-patients-with-donors/how-donors-and-patients-are-matched/hla-basics/	Human leukocyte antigen (HLA) typing is used to match patients and donors for bone marrow or cord blood transplants. HLA are proteins—or markers—found on most cells in your body. The immune system uses these markers to recognize which cells belong in your body and which do not.
Human Leukocyte Antigens (HLA) https://www.cancer.gov/publications/dictionaries/cancer-terms/def/human-leukocyte-antigen	A type of molecule found on the surface of most cells in the body. Human leukocyte antigens play an important part in the body’s immune response to foreign substances. They make up a person’s tissue type, which varies from person to person. Human leukocyte antigen tests are done before a donor stem cell or organ transplant, to find out if tissues match between the donor and the person receiving the transplant. Also called HLA and human lymphocyte antigen.
Precision Medicine Initiative (PMI) https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative	A research initiative funded by the President’s 2016 Budget to pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients.
Part B. Form of ASTM Specifications https://www.astm.org/FormStyle_for_ASTM_STDS.html	A specification is an explicit set of requirements to be satisfied by a material, product, system, or service.
Versiti https://www.versiti.org/home	Versiti is an affiliation of healthcare organizations with the vision to improve the health of patients through innovative transfusion solutions for healthcare systems. It is home to the Blood Research Institute, that enables life-saving gifts from donors, and it provides the science behind the medicine through its diagnostic laboratories.

