The Office of the National Coordinator for Health Information Technology

Sync for Genes Phase 2 Project

EXPLORING APPROACHES TO MAKE CLINICAL GENOMICS AVAILABLE AT THE POINT-OF-CARE

FINAL REPORT

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EXECUTIVE SUMMARY

Introduction

Under direction from the Office of the National Coordinator for Health Information Technology (ONC), the Sync for Genes Phase 2 (Phase 2) project continued the goal of Sync for Genes Phase 1 by further exploring approaches of exchanging and integrating genomic data into healthcare systems and for research. Sync for Genes Phase 2 tested and refined the Health Level Seven International® (HL7®) Fast Healthcare Interoperability Resources (FHIR®) Clinical Genomics specification by pilot testing the standard, providing feedback for the refinement of the specification directly to the HL7 Clinical Genomics Work Group, and participating in a FHIR Connectathon.[1,2,3]

Pilot Testing

Four organizations participated in Phase 2 to pilot test the use of standards for the exchange and integration of genomic test results at the point-of-care. Those organizations were the Utah Newborn Screening (NBS) Program, Weill Cornell Medicine (WCM), Lehigh Valley Health Network (LVHN), and the National Marrow Donor Program (NMDP). Each organization proposed a unique use case that used HL7 standards to share genomic data. Use cases were based on genomic results obtained through next generation sequencing (NGS) techniques and represented a variety of scenarios pertaining to newborn screening, supporting the availability of point-of-care knowledge resources, cancer pharmacogenomic testing, and donor matching. Each organization mapped workflows illustrating their unique genomic use case to FHIR and, based on their experience, provided feedback for the refinement of the FHIR Clinical Genomics specification.

Participation at the HL7 FHIR Connectathon

Three of the four pilot sites participated in the January 2019 HL7 FHIR Connectathon. This two-day event is a hands-on development activity intended to test FHIR. The pilot sites participating in the Connectathon successfully demonstrated connectivity and exchange of clinical genomic data using the FHIR Clinical Genomics specification and their own genomic diagnostic reports.

Challenges

As part of the Phase 2 project, pilot sites identified challenges specific to currently available standards and within the genomic industry that must be addressed to fully and securely enable the use of genomic data for the provision of care and for research. Challenges regarding the implementation of the currently available standards included missing or mis-aligned semantics, the need for diverse community representation in standard development organizations, and the need for an understanding of the complexities of the genomic field among developers and implementers. Challenges that are relevant to the genomics industry at-large include needed alignment among legislation or policies that address privacy issues; security; data provenance; data storage and management; educational support for providers and patients; clinical and laboratory information systems that are not designed to accommodate the complexities of genomic use cases; health information technology (health IT) developer[1] readiness to implement FHIR; and cost and business drivers.

Lessons Learned

The work conducted under Phase 2 provided valuable lessons regarding the importance of appropriately scaling and scoping projects related to the exchange of genomic data; having working knowledge of FHIR and genomics;

[1] http://hl7.org/fhir/
[2] http://www.hl7.org/
[3] http://www.hl7.org/Special/committees/clingenomics/index.cfm

understanding the current health IT developer support of FHIR; and the need for additional guidance and documentation to support the interoperable implementation of standards.

INTRODUCTION

The role and power of genomic data have become an increasing area of focus in healthcare research and delivery. Programs such as the *All of Us* Research Program and the vision of the 21st Century Cures Act depend on the ability to leverage genomics to shape the future of healthcare. [4,5] There are challenges that must be overcome before these data can be integrated into and used by healthcare systems and the research enterprise. To be available at the point-of-care, genomic data must be represented consistently so that health IT, such as electronic health record (EHR) systems, can easily incorporate those data in a consistent way.[6] Similar to other health data, genomic data must also be shareable to facilitate a patient's relationship with his or her team of providers, genetic counselors, and loved ones. Shareable data supports patients in making informed healthcare decisions and decisions about when and how to share this sensitive and information-rich data with researchers. Since 2016, ONC has worked in partnership with the National Institutes of Health (NIH) on the Sync for Genes project to make genomic data available at the point-of-care and for research. [6] Similarly, ONC has partnered with NIH on Sync for Science, a project that developed and tested a simple way for people to share their health data with researchers.[7] The Sync for Genes goal of making clinical genomic data available within EHRs, can pave the way for patients to share genomic information with researchers using the technology developed by Sync for Science.

The Sync for Genes Phase 1 project made great strides in standardizing the way genomic data can be exchanged electronically. Sync for Genes Phase 1 leveraged the Health Level Seven International® (HL7®) Fast Healthcare Interoperability Resources® (FHIR®) standard to test and validate HL7 FHIR Clinical Genomics artifacts (e.g., implementation guide, profiles). [8,9,10] This collaboration with HL7 established a robust framework to continue testing the use of standards like FHIR to exchange and integrate genomic data into the healthcare system.

The next phase of this project, Sync for Genes Phase 2 (Phase 2), which launched in 2018, built upon the work of Sync for Genes Phase 1 by further exploring different facets of the original goal: making genomic data available at the point-of-care and for research. This report summarizes the Phase 2 project goals, pilot testing approach, participating organization overviews and use cases, project outcomes, and how this work informed the continued development of the FHIR Clinical Genomics specification. The report also identifies challenges the pilot projects encountered during the course of this project and summarizes lessons learned.

Background and Overview

The rise of genomic testing and the potential for genomics to shape clinical care has implications across the healthcare continuum. While the potential is exciting, realizing this potential can often be daunting and overwhelming. Making the vision of the 21st Century Cures Act a reality through activities under the Precision Medicine Initiative (PMI) such as *All of Us,* requires integration of clinical genomics as a routine part of the care continuum.[11] ONC continues to support these programs and initiatives with projects like Sync for Genes, that advance the use of standards like FHIR for data sharing.

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[5] https://allofus.nih.gov
[5] https://www.congress.gov/114/plaws/publ255/PLAW-
[6] https://www.healthit.gov/topic/sync-genes
[7] https://www.healthit.gov/topic/sync-science
[8] http://www.hl7.org/
[9] http://hl7.org/fhir/
[10] http://www.hl7.org/Special/committees/clingenomics/index.cfm
[11] https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

PILOT TESTING APPROACH

Pilot testing and implementing a specification are necessary to develop and advance a standard. This helps uncover gaps and reveal challenges that a standards development organization can use to refine the standard. Based on the work in the previous Sync for Genes Phase 1 pilot projects, recommendations from federal partners, and input from subject matter experts, ONC decided to proceed with Phase 2. ONC identified four organizations to participate in Phase 2. The organizations represented academia, research, and non-profit organizations and featured a heterogeneous set of use cases. The organizations' use cases were diverse, each with different goals and leveraging different data sources. Despite differences, the four use cases all shared elements identified in the FHIR Clinical Genomics Domain Analysis Model (DAM), which is published and maintained by the HL7 Clinical Genomics Work Group. [12] The DAM outlines various use cases specific to the clinical genomics field (e.g., preimplantation genetic diagnosis, whole exome sequencing, RNA-sequencing, and proteomics) that should be supported by the FHIR Clinical Genomics specification. Each participating organization had or produced designs for their workflows and then began the process of mapping them to the FHIR Clinical Genomics Standard for Trial Use (STU) 3 (FHIR R3.x). Three of the four Phase 2 pilot sites tested the FHIR Clinical Genomics specification in different ways. The fourth pilot site tested the use of the HL7 V2 messaging standard. [13,14]

Participating organizations provided feedback on both the DAM and the FHIR Clinical Genomics specification through several mechanisms. This feedback was a crucial step in advancing the FHIR Clinical Genomics specification from STU 3 to STU 4. The following sections include descriptions of the pilot project use cases, activities, and outcomes of each of the four pilot sites that participated in the Phase 2 project.

PARTICIPATING ORGANIZATIONS AND USE CASES

Lehigh Valley Health Network

The Lehigh Valley Health Network (LVHN) Cancer Center delivers full comprehensive services and advanced oncology care to its members, including genomic testing. LVHN is a member of the Memorial Sloan Kettering Cancer Alliance. The goal of this pilot project was to integrate genomic sequencing into the EHR and clinical workflows for better-targeted treatments.

Lehigh Valley Health Network Pilot Narrative

A patient is informed of a hormone-receptor-positive, early-stage breast cancer diagnosis. The provider asks about a family history of hormone-receptor-positive breast cancer and if any family members have had issues with treatment (e.g., Tamoxifen). The patient relates a positive family history for this type of cancer, but is unsure about a drug reaction. The provider suggests pharmacogenomic testing before starting the treatment and orders a blood draw for the drug-gene pair analysis. The information regarding a drug-gene interaction based on the genomic test results are sent to the EHR while the complete results of the genomic test are sent to a data warehouse, where they are accessible for future use. The provider is notified when the results are available. The provider then orders the best suited medication as informed by the results from the drug-gene analysis.

Lehigh Valley Health Network Pilot Description

LVHN uses genomics as a critical element of diagnosing and treating many types of cancer. In this pilot project, LVHN leveraged an HL7-based solution that can link clinical phenotype information to enter genomic data into the EHR. The team also implemented the workflow necessary to trigger clinical alerts when genomic test results

[12] http://www.hl7.org/implement/standards/product_brief.cfm?product_id=479
[13] https://www.HL7®.org/FHIR®/genomics.html
[14] https://www.hl7.org/implement/standards/product_brief.cfm?product_id=185

indicated a drug-gene pair issue. For example, an alert would be created if a genomic test result indicated that a patient may be less likely to respond to a selected drug. LVHN reviewed the Food and Drug Administration data regarding genetic implications as the first step in developing a list of candidate medications for this pilot project. LVHN also used other sources, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC®), to aid in determining the most common drug-gene pairs.[15]

Lehigh Valley Health Network Pilot Outcome

Based on the review of LVHN genomic data sharing partners (e.g., laboratory systems, clinical information systems) and an anticipated upgrade to the newer version of their EHR system, LVHN decided to leverage HL7 v2.2 instead of FHIR. By the end of the project period, the team had included three drug-gene pairs and the accompanying laboratory tests into their current version of their EHR. The team expected to continue modification as necessary once their EHR system upgrade is complete. The team will continue to use CPIC as the baseline for identifying drug-gene pairs to integrate into their system, with a focus on oncology drugs.

Similar to other pilot projects, this project's outcomes were highly dependent on whether the clinical and ancillary systems (e.g., laboratory) were able to implement FHIR and the decision to wait for an anticipated EHR system upgrade that included a genomic module. Additionally, LVHN noted skepticism among some providers about the use of pharmacogenomic data. This team echoed the need for additional targeted and timely training to support providers in both understanding this new source of health information and how to best use these results to facilitate decision-making with their patients.

National Marrow Donor Program

The National Marrow Donor Program (NMDP) collects NGS-based human leukocyte antigen (HLA) genotyping information using Histoimmunogenetic Markup Language (HML) formatted reports. The goal of this pilot project was to enhance a tool that converts existing information being collected as HML into FHIR-based resources without losing the completeness of the information currently being captured.

National Marrow Donor Program Pilot Narrative

As part of a donor drive, an individual is tested and to be included in a catalog as a potential stem cell donor. The donor registry organization swabs the inside of the individual's cheek to collect the sample. An order for HLA genotyping is sent to a laboratory along with the sample. The laboratory sequences exons 2 and 3 of the HLA genes. The laboratory may also conduct full gene sequencing. The test results are uploaded into the HML portal and converted to HL7 FHIR as a transaction bundle consisting of the final report; the supporting information, including the evidence leading to genotyping for each gene; identification of separate alleles; and sequencing data for each exon. The laboratory results and supporting information are sent to a repository for storage and use. The data that is available in a FHIR format facilitates its use for matching donors to recipients, as well as for research purposes.

National Marrow Donor Program Pilot Description

For this pilot project, NMDP used HLA genotyping data in HML format from the Stanford Blood Center that was collected as part of the 17th International HLA & Immunogenetics Workshop. NMDP converted the HML-formatted reports to FHIR R3 using HML2FHIR®, which is a tool NMDP developed, and the Genomics Reporting Implementation Guide.[16] Although the Genomics Reporting Implementation Guide is based on FHIR R4, it can be used to inform mappings to R3. This mapping included obtaining information about the specimen tested, the laboratory test performed, the loci targeted, the consensus sequences found, and the alleles assigned. This work

[15] https://cpicpgx.org/
[16] http://www.hl7.org/FHIR/genomics.html

tested the completeness of resources in the FHIR Clinical Genomics specification and validated the rigor of the FHIR resources as they are used in clinical genomics. The comparison between HML and FHIR messages helped identify missing data elements, or data elements being referenced in the wrong FHIR resource.

National Marrow Donor Program Pilot Outcome

NMDP developed a version of the HML2FHIR tool prior to participating in the Phase 2 pilot project. During the Phase 2 pilot project, NMDP confirmed that the HML2FHIR tool functioned and constrained it to address some of the ambiguity regarding the optionality within HML. This helped demonstrate the alignment of the tool with the FHIR Clinical Genomics specification and the NMDP rules for submitting HML to NMDP. The project team used the principles described in the HL7 Clinical Genomics Implementation Guide to validate the conversion produced by the HML2FHIR to both the FHIR R3 and FHIR R4 formats. For example, these principles note the use of components instead of extensions as outlined by FHIR R4. This was another step toward a production-ready version of HML2FHIR. During the course of this project, NMDP found that there are insufficient provenance resources available for clinical genomics use cases, noting the importance of knowing the original source of the data and genomic diagnostic report.

In the future, NMDP expects to move this proof of concept tool into a production environment complete with dedicated resources and organizational strategy to support this endeavor. At that time, NMDP can test the tools in a production environment partnering with organizations to send real patient genomic data via the HML gateway and using HML2FHIR conversion tool to convert the HML formatted data to FHIR.

Utah Newborn Screening Program

The Utah Newborn Screening (NBS) Program is a program within the Utah Department of Health. The Utah NBS Program is in the process of developing a whole exome sequencing platform for second- and third-tier molecular testing following abnormal biochemical testing. The goal of the Utah NBS pilot project was to develop a proof of concept model and method to share raw genomic data in a standardized way with external healthcare partners and providers at the point-of-care.

Utah Newborn Screening Program Pilot Narrative

In the near future, all parents of babies born in Utah may consent to second- and third-tier molecular testing for babies with abnormal initial biochemical screening assay results that are indicative of a disorder monitored by the Utah NBS Program. This proposed workflow assumes the involved health IT systems are capable of exchanging FHIR-based messages.

The initial biochemical screening is conducted by collecting a dried blood spot (DBS) specimen from the newborn. The healthcare provider submits an order for this newborn screening that is entered into the EHR system. A newborn screening laboratory receives the order along with the specimen, processes the specimen, and performs the necessary biochemical screening tests. An abnormal result may indicate the need for further genomic testing, prompting the need for second- or third-tier molecular testing. The second-tier genomic test (whole exome sequencing) targets any disease variants associated with the suspected disorder. The results are compiled and sent to a data repository. At the same time, an HL7 v2.5 message that includes all of the NBS results is sent to the Clinical Health Information Exchange (CHIE), Utah's health information exchange. The CHIE disseminates the information to the appropriate entities, such as requesting birth hospitals and providers, using HL7 FHIR messages, HL7 v2.x messages, or a web portal. If the provider would like the test results as discrete data to integrate into the clinical record for further analysis, the provider may request the results in the form of an HL7 FHIR message.

Utah Newborn Screening Program Pilot Project Activities

As part of the Phase 2 pilot project, the Utah NBS Program used the FHIR Clinical Genomics specification to test the ability to send genomic diagnostic report results as FHIR messages to authorized institutions and providers.

This work leveraged existing resources and expertise from a participant from the Sync for Genes Phase 1 at Intermountain Healthcare. The team confirmed that their data partners were able to accept FHIR messages and were interested in receiving genomic test data as discrete elements. The Utah NBS Program performed all sequencing tasks as well as all relevant sequence analyses. A FHIR application programming interface (API)**Error! Bookmark not defined.** and related infrastructure was used to produce FHIR requests for genomic-related information. Upon receiving a FHIR request, the Utah NBS Program produced a FHIR R3 compliant message to fulfill the request.

Utah Newborn Screening Program Pilot Outcome

The Utah NBS Program created FHIR R4 messages based on those FHIR R3 messages. They also successfully demonstrated the sharing of genomic diagnostic reports in a test environment. The team at the Utah NBS Program continues to work with their partners through contractual and business issues related to the exchange of genomic data.

The technical challenges this team encountered while implementing the FHIR Clinical Genomics specification include the need for:

- Guidance regarding which FHIR resource or resources should be used to attach files, such as Variant Call Format (VCF), that allows for the level of specificity and granularity needed for re-analysis.
- Guidance regarding the representation of genomic concepts when using FHIR resources, which were originally developed with non-genomic use cases in mind.
- Harmonization of data element definitions between clinical genomics and FHIR.
- Documentation and examples of complex use cases like those found in clinical genomics.

Perhaps the most significant and pressing challenge for the NBS team were issues regarding health IT developers' readiness and ability to adopt FHIR. These issues extend from laboratory systems willing to send results as FHIR messages to healthcare organizations' readiness to implement production systems that could send and receive FHIR messages. One facet of this challenge was the ability for the program itself to procure the needed health IT infrastructure to store large genomic files and FHIR servers to exchange FHIR messages within the Phase 2 timeframe.

Weill Cornell Medicine

Weill Cornell Medicine (WCM) is a quaternary care academic medical center, participating in the *All of Us* Research Program. Weill Cornell Medicine has an institute of precision medicine with a focus on advanced cancers. The overarching vision for their pilot project was to use discrete genomic results in a variety of clinical decision support scenarios. The scenarios WCM considered included point-of-care knowledge support, pharmacological therapy selection, research recruitment, and navigating insurance and pre-authorization requirements for genomic testing. The WCM team narrowed the scope of their project to address point-of-care knowledge requirements to support provider discussions with patients regarding NGS results.

Weill Cornell Medicine Pilot Narrative

A provider requests an EXaCT1 test for a patient that is diagnosed with metastatic bladder cancer. This test can help the provider determine if the patient's tumor has any genetic variants that would be responsive to certain chemotherapeutic or immunotherapeutic agents. EXaCT1 is a New York State Clinical Laboratory Improvement Amendments (CLIA) approved laboratory-developed test for whole exome sequencing. The request for this test is entered into the EHR system and sent to a molecular pathology laboratory. The laboratory generates variant results as pathogenic, likely pathogenic, and those of unknown significance, along with several discrete components pertaining to each of the altered genes. The provider is able to see the pathogenic and likely

pathogenic variant results in the EHR. Variants of unknown significance are stored in an external repository because of architectural constraints against diminishing returns of storing the data in the EHR. The provider is able to query external genomic knowledge resources against results stored in the EHR, as well as those stored in the external repository, directly from their EHR using a connection via a FHIR API. This point-of-care knowledge support can present provider and patient educational materials that include information on companion therapeutics.

Weill Cornell Medicine Pilot Description

Oncology-specific genomic testing and approved medications by cancer type are still evolving. They are extraordinarily complex, and such information lies in disparate sources (e.g., EHRs, treatment guidelines, and in payer databases). One objective of this project was to create workflow maps that illustrate the use HL7 FHIR to make discrete genomic results available for a variety of oncology-specific scenarios. To develop these workflow maps, the pilot project demonstrated how they could leverage WCM's existing comprehensive EHR infrastructure that currently interfaces with their genomic data system. The WCM team is also developing a modular app, that serves as a FHIR-enabled platform to combine information from external knowledge sources, such as ClinVar, and mapping this resource to the FHIR specification with genomic results.[17] Such point-of-care knowledge can facilitate provider-patient relationships and guide decision-making.

Weill Cornell Medicine Pilot Outcome

By narrowing their use case to point-of-care knowledge support, WCM focused on a subset of components in the FHIR Clinical Genomics specification. This lessened the overwhelming nature of moving entire, complex workflows to FHIR. The team was better able to determine a strategy and process that considered the implementation of an EHR genomic module and for moving beyond the point-of-care knowledge use case to an enterprise-level endeavor. WCM expected to continue mapping additional clinical genomic use cases to FHIR as their EHR developer implemented the new genomic module.

HL7 FHIR CONNECTATHON

In addition to conducting individual pilot projects, three of the four organization participated in the Clinical Genomics track of the HL7 FHIR Connectathon in January 2019. An HL7 FHIR Connectathon is a 2-day event held in conjunction with HL7 Working Group meetings. FHIR Connectathons provide an excellent opportunity for implementers and developers to gain hands-on experience with FHIR-based solutions by participating in tracks designed around FHIR components, work groups, or implementation topics.[18] The goal of the Scenario 10: Implementing Genomics Diagnostic Report track at the 2019 FHIR Connectathon was to test the FHIR Clinical Genomics specification by demonstrating the exchange of genomic diagnostic reports.[19]

Connectathon Preparation

In preparation for the Connectathon, each organization selected a genomic diagnostic report containing genomic test results from their own organization. Pilot sites brought samples of diverse reports. Once the reports were selected, each project identified key data elements in the report and mapped them to FHIR resources and profiles. Using their respective site-specific mappings, each organization developed FHIR renderings of the data contained within their genomic diagnostic reports. The output of these renderings was an eXtensible Markup Language (XML) file, which was used at the Connectathon to demonstrate the exchange of genomic data between preconfigured FHIR servers to validate the mapping.

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[17] https://www.ncbi.nlm.nih.gov/clinvar/

[18] http://www.hl7.org/events/fhir-connectathon/index.cfm

[19] https://wiki.hl7.org/Category:201901_FHIR_Connectathon_Track_Proposals

To prepare for the Connectathon, pilot sites completed these four steps, as illustrated in Figure 1 below:

1. Identify a genomic diagnostic report (e.g., newborn screening genomic diagnostic report).
2. Identify the data elements in the report necessary for exchange (e.g., date collected).
3. Map data elements from the report to FHIR (e.g., "Date Collected" maps to "effectiveDateTime" in the DiagnosticReport FHIR resource).
4. Create XML files based on the FHIR mapping of the genomic diagnostic report.

Connectathon Activities

Phase 2 created Scenario 10: Implementing Genomics Diagnostic Reports.[20] An objective of this scenario was to identify the types of local modifications each pilot site required when implementing FHIR Clinical Genomics resources. This work also uncovered gaps in the FHIR Clinical Genomics specification.

The Phase 2 scenario included two main activities:

1. Sending the FHIR message (in the form of an XML file) to other participating organizations' test FHIR servers
2. Demonstrating the accurate receipt of each data element in the FHIR message
3. The participants also attempted to link all three genomic diagnostic reports and send the linked version in a consolidated report.

20 http://wiki.hl7.org/index.php?title=201901_Clinical_Genomics#Scenario_10:_Implementing_Genomics_Diagnostic_Reports

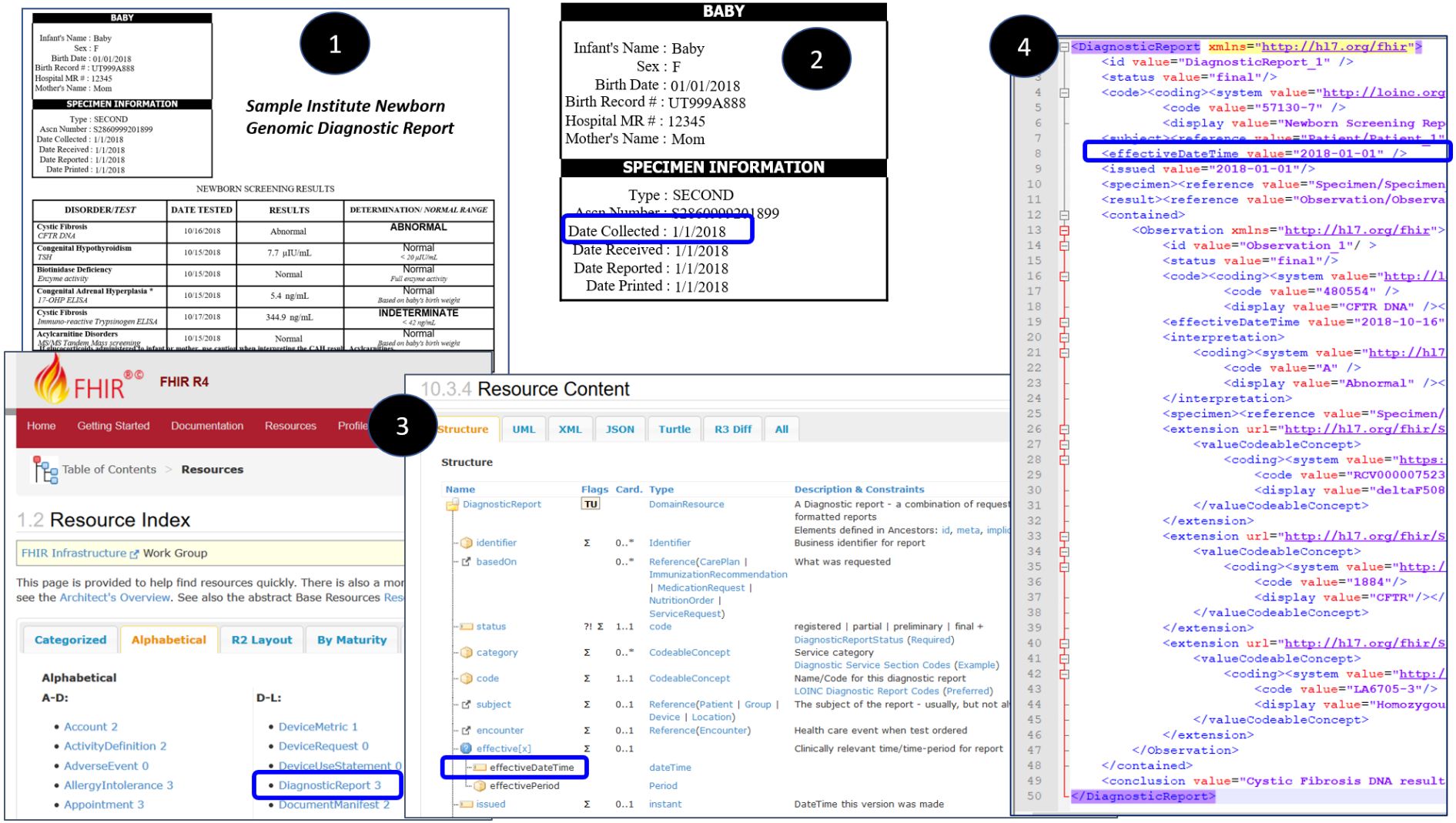

Figure 1. Connectathon Preparation

Connectathon Outcomes and Identified Gaps

The three participating organizations successfully exchanged a FHIR-based version of their genomic diagnostic reports (XML files) with each other during the Connectathon. This was a significant accomplishment for both the pilot sites and FHIR Clinical Genomics. This successful exchange validated the FHIR Clinical Genomics resources and aided in finding areas where these resources are lacking or need additional modifications. The XML files generated and used by each of the pilot sites are listed in Appendix A of this report and are available on the HL7 Connectathon Wiki. These files can be used as samples by developers. Participation in the Connectathon also identified gaps in the specification, which are discussed in detail below.

Guidance and Documentation Gaps Identified During the HL7 Connectathon

The FHIR Clinical Genomics specification is ambiguous and lacks clear guidance when there are multiple ways to represent a concept in FHIR. This void creates inconsistencies between implementations and makes interoperability difficult. Therefore, there is a need for comprehensive guidance and additional documentation or examples for implementers to reference. For example, it is unclear how to use FHIR to bundle multiple resources into a single XML message. Although the ability of existing FHIR resources and profiles to support the exchange of genomic diagnostic reports was validated in some areas, the teams found several gaps. As more samples of laboratory reports are mapped to FHIR, particularly reports with multiple results, this can help inform the development of robust guidance for the application of FHIR to the exchange of genomic diagnostic reports.

Additionally, genomic use cases present complexities that the standards development community may not fully be aware of but will need to address. Currently, FHIR does not provide best practices for the representation of complex workflows, such as one diagnostic report referencing another diagnostic report. As genomic testing and genomic knowledge improves there may be a need to retest patients. It is currently unclear how FHIR would be able to support a reference within a new diagnostic report to previous reports.

Similarly, current FHIR guidance does not describe how the standard could support the identification of whether test results are part of a subset of a larger genomic test. The extensive and—sometimes—large nature of genomic test results may contain more data than the provider wants or needs at the time of the report. For example, a multigene panel can include a varying number of genes for analysis. A developer may use the FHIR resource "observation" to represent this multigene panel. However, the challenge is that "observation" does not allow for the granularity needed to determine which observation—or, in this case, which one of the genes included in the multigene panel—is being referenced. The resource "observation" could also be used to reference a collection of genes or the complete set of genes in the multigene panel. In many cases, a provider receives a subset of a genomic test, with only the data needed at that time. However, after viewing those results, a provider may want to know the entirety of what was tested. This issue is of particular interest to the genomic community as diagnostic technologies, interpretation, and genomic science are still evolving, and the roles different genes have in disease presentation can change over time.

Finally, during the Connectathon, the pilot sites found that the FHIR Clinical Genomics specification does not identify how to capture metadata or granular information about the genomic data, such as what region(s) of the genome was targeted for testing, what region(s) were actually tested, what was observed, and what was reported. In FHIR, the semantic representation of terms, such as "location" and "observation," tend to serve clinical needs and therefore do not always accurately represent the needs of genomic use cases. For example, in FHIR R4, the "location" resource refers to a physical location, such as a building or a laboratory. In the genomic domain, "location" may specify the coordinate location of genetic features on a chromosome reference sequence. Similarly, the FHIR R4 "observation" resource is intended to capture clinical observations, such as those made during a physical exam or the result of a traditional laboratory test.

PROVIDING FEEDBACK TO HL7 TO ADVANCE THE FHIR CLINICAL GENOMICS SPECIFICATION

Phase 2 supported the refinement of the FHIR Clinical Genomics specification by providing feedback that resulted directly from pilot projects and participation at the HL7 Connectathon to the HL7 Clinical Genomics Work Group. Feedback was collected during monthly pilot project meetings where teams discussed progress and the challenges or successes they encountered when using the FHIR Clinical Genomics specification. The mechanisms used to provide this feedback included the following:

- Participation in the HL7 Clinical Genomic Work Group meetings
- Utilization of HL7 message boards and messaging tools such as Zulip
- Formal ballot comments to the base HL7 FHIR R4 standard and FHIR Clinical Genomics specification ballot
- Other activities as suggested by the HL7 Clinical Genomic Work Group

This feedback provided by the organizations leading Phase 2 pilot projects supported the advancement of the FHIR Clinical Genomics specification from STU 3 to STU 4. For example, the HL7 Clinical Genomics Work Group accepted the comments to the ballot regarding this issue of bundling resources and will be addressing it in future iterations of the FHIR Clinical Genomics specification.

ADDITIONAL CHALLENGES

Operationalizing the integration of genomic data into the clinical and research environment is a relatively new undertaking for most healthcare organizations. Healthcare organizations often face challenges in integrating silos of health information to provide coordinated, comprehensive care. Integrating genomic data has proven to be no different. In addition to the gaps the pilot projects uncovered as they put the technology into practice for the exchange and integration of genomic data, there are larger challenges that will need to be addressed by a broader group of stakeholders interested in the use of genomics for healthcare delivery and research. These challenges are separated in the next two sections and identified as Health IT Standards Challenges and Genomic Industry Challenges.

Health IT Standards Challenges

Much work has been done to develop semantic (language) and syntactic (exchange) standards that support the sharing of genomic data. The HL7 Clinical Genomics Work Group has laid a foundation for sharing genomic data through the following:

- The HL7 Domain Analysis Model (DAM) for Clinical Genomics: The DAM is a set of high-level genomic use cases that capture the unique needs of clinical genomics for data exchange.
- The FHIR Clinical Genomics Implementation Guide: This implementation guide provides direction on how to implement the FHIR Clinical Genomics specification.

While these resources exist to help implementers and the community better understand how genomic use cases are represented in FHIR, the progress and maturity of the specification depends on the testing, validating, and contributions made by participants of programs such as Sync for Genes. Table 1 includes the three challenge areas that should be addressed to support the continued development of the FHIR standard and its application to genomics.

Table 1. Health IT Standards Challenges

Challenge Area	Scope
Semantics	Genomic semantic challenges exist at two primary levels: 1. Genomic concepts vs. non-genomic (clinical) concepts 2. Semantic differences within genomics (e.g., classical genomic semantics vs. NGS semantics)
Greater community representation in the standards development process	The current FHIR Clinical Genomics specification is driven by those represented in the work group. More participant diversity is needed to ensure that the specification has the rigor necessary to continue to support the integration of genomic data.
Training	Education and support are needed to help implementers understand and utilize the FHIR Clinical Genomics specification.

Modeling Efforts and Semantics

Although significant progress has been made in collecting and representing genomic use cases, Phase 2 and the resulting pilot project outcomes have shown that additional detail in the semantic representation of genomic use cases is needed. Figure 2 below represents the iterative process of how the FHIR Clinical Genomics specification is informed by the DAM, along with the identification and modeling of semantic concepts.

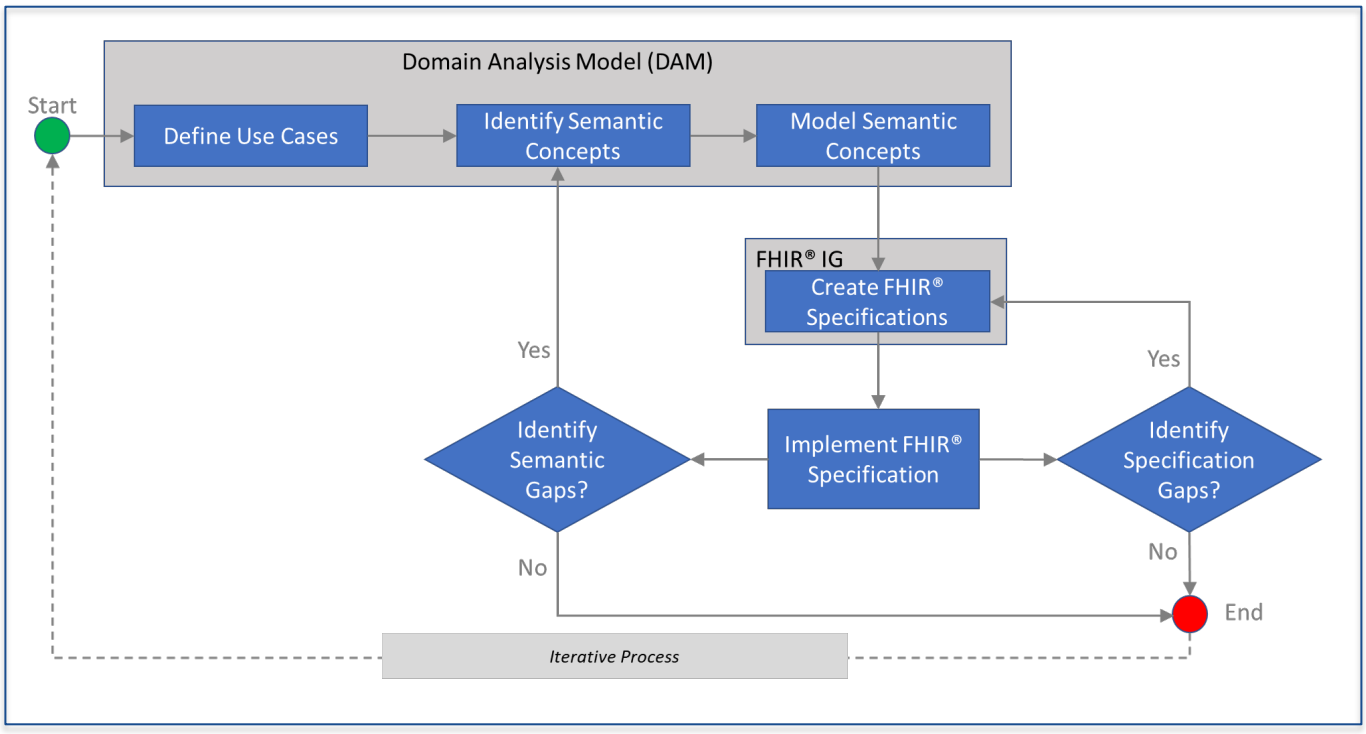

Figure 2. Process of Identifying and Modeling Semantic Concepts and Creating a Standard Specification

The lack of well-defined semantic concepts and a common genomic data model has resulted in numerous "micro-domains," which have produced unique data models and home-grown standards. This creates potential challenges to interoperability requiring significant human intervention and mapping.

As previously mentioned, FHIR may identify "location" as a physical address or a location on the body as in the event of a surgical procedure (e.g., left kidney, right leg). However, in genomics, "location" may point to a band location, location on a sequence, or location of a reference sequence. While the concept of "location" is used in both instances, it does not have the same meaning. Further defining the concept of "location" helps add clarity to the term and provides a way in which clinical information systems can integrate the genomic concept of "location" into their system.

Another semantic challenge occurs within the genomic domain itself. There are instances when a single genomic term can be defined and used differently. For example, there is ambiguity with the term "allele." A classical geneticist may say "allele" referring to an entire genetic locus and everything included with that locus. An NGS geneticist might think of an "allele" as an individual single genetic variant. Within the genomic domain, there are also examples where two different terms are used to mean the same thing. For example, when modeling the different types of variation that occur in a genetic panel, copy number can be recorded as duplication (DUP) or copy number variant (CNV). Each term means the same thing, but different phrases are used.

Structured, well-defined semantics, represented through a data model, provide implementers with the level of detail necessary to integrate the nuances of genomics into health information systems such as EHRs. As a result of identification of this challenge during the Phase 2 project, ONC supported a small project to re-initiate development of a conceptual information model that is technology agnostic and promotes consistency among the standards used by the HL7 Clinical Genomics Work Group. At of the end of this project, this work was transferred to the HL7 Clinical Genomics Work Group, which oversees standards development for the clinical genomics domain.

Greater Community Representation of the HL7 FHIR Standard

Achieving widespread use and adoption of both genomic data and FHIR is complex and requires implementation and testing by a broad range of community members with differing needs and perspectives. The development of a standard such as FHIR relies on volunteers, developers, implementers, health IT developers, users, business analysts, and patients. There is a need for more diverse representation in the standards development process. Interested stakeholders may find entry into this process by participating in work groups.[22] Greater representation in the standards development process by the diverse set of stakeholders that will be affected by the use of clinical genomics for care and research can lead to better solutions that meet their varying needs.

Bridging Clinical Genomics and FHIR Experience

Understanding genomic-specific use cases, harmonizing semantics, and mapping them to FHIR can be overwhelming, especially if a developer, modeler, or implementer is unfamiliar with either FHIR or genomics. This project used a small cohort style and introduced participants to subject matter experts from the genomic and FHIR fields to help participants bridge their expertise in clinical genomics with FHIR. The varying levels of experience with FHIR of the organizations participating in Phase 2 highlighted the value of targeted support. A continuation of this model, cohort-style projects, or through smaller, genomic-focused events that combine didactic high-level genomic overviews and FHIR training, could be an effective way of expanding the cadre of experts who can leverage expertise in clinical genomics and FHIR. To solidify acquired skills, projects or events should include an opportunity for participants to apply their learning to a demonstration of genomic data exchange. This hands-on application, which occurred during the HL7 Connectathon, was a critical component of the Sync for Genes project. The organizations that participated in Phase 2 pilot projects also suggested that establishing a mentor and mentee program would be beneficial to further the adoption of FHIR for clinical genomics. The group found that the small-

[22] http://www.hl7.org/special/committees/index.cfm

group interactions facilitated by Phase 2 and the opportunity to apply the specification to clinical genomic use cases in a guided environment were effective ways of knowledge sharing, honing skills, and overcoming barriers.

Genomic Industry Challenges

Current industry challenges that were identified by Phase 2 and are summarized in Table 2, impact all parts of the care delivery system, including health IT developers, providers, patients, and researchers. Although out of scope for this project, they are included in this report to provide context for the current landscape of the field of genomics and to highlight the importance of a multifaceted approach to the goal of making genomic data available at the point-of-care and for research.

Table 2. Genomic Industry Challenges

Challenge	Description
Alignment of legislation or policies that support privacy (e.g., Health Insurance Portability and Accountability Act [HIPAA],[22] Title 42 of the Code of Federal Regulations Part 2 [42CFR Part2])Error! Bookmark not defined.,[23]	Legislation and policies intended to protect patient privacy may not be expansive or focused enough to reflect protection concerns for genomic data because they were established before genomic data were available for integration into clinical information systems.
Security	Industry accepted security standards are necessary for all the systems that order, test, analyze, store, and present genomic data.
Data provenance[24]	Mechanisms to provide provenance information for genomic data (e.g., origin, ownership, custody, and interpretation of the data) can be challenging to develop due to the complexities and analysis necessary to return a genomic laboratory result.
Data storage and management	Most clinical information systems were not designed to support the large amount of data that genomic tests typically yield, therefore strategies to integrate (fully or partially), manage, and display genomic test result data in ways clinical information systems and end users can consume are needed.
Educational support for providers and patients	Training and education is needed to help providers communicate the value and results of genomic tests to their patients. Patient education is also important to support them and their caregivers in understanding results and their implications.
Clinical and laboratory information systems are not designed to accommodate the complexities of genomic use cases	Complex genomic use cases are difficult to integrate into clinical or typical laboratory information systems because those systems were not created to support genomics (e.g., differentiating between the genomics of the donor kidney and a recipient's deoxyribonucleic acid [DNA] when the kidney is part of the recipient).
Health IT developer capabilities to implement FHIR	The adoption of FHIR is variable among health IT developers.

[22] https://www.hhs.gov/hipaa/for-professionals/privacy/index.html
[23] https://www.govinfo.gov/content/pkg/CFR-2017-title42-vol1/xml/CFR-2017-title42-vol1-part2.xml
[24] https://nnlm.gov/data/thesaurus/data-provenance

Challenge	Description
Cost and business drivers	Alignment of organization priorities, funding, and resources to procure and support systems for genomic uses cases is necessary.

Alignment of Legislation and Policies that Support Privacy

Clarity is needed regarding how genomic data are protected as they are collected, used, and stored. A genomic profile is a more comprehensive identifier than fingerprints, a social security number, or other unique identifiers. Fundamental questions regarding genomic data and their use remain. For example, answers seem to evolve over time for questions regarding who can see these data, for what purpose, and how to manage the data. Currently, the greater community has not determined whether or how data regarding protected class illnesses such as schizophrenia—which could potentially be inferred based on genomics[25]—could be segmented, or if it should be altogether removed from a genomic profile. Although there are standards available to address the technical aspects of privacy, there is no industry agreement with respect to how those standards should be applied to the policy and ethical challenges that are unique to the science of genomics. A thorough analysis of current legislation and policies (e.g., HIPAA, 42 CFR Part 2) with regard to genomic-specific concerns is needed. This analysis and the resulting outcomes should be represented in the FHIR Clinical Genomics specification, ensuring the specification provides the necessary security to exchange data with more points of user identification than what clinical information systems currently support.

Security

Access control and security standards exist and are generally effective in clinical information systems that use them. It is important to validate that appropriate access controls exist for the sharing of genomic data, whether genomic data are stored "in house," in external, or in third-party systems that can be accessed by one or many other clinical or research systems.

Data Provenance

Contextual information about genomic data, which can include information regarding consent of their use, should be available with the data, given the identifiable nature of the genomic data. Provenance information can protect a patient's privacy preference and provide valuable information to providers and researchers. For example, a provider or researcher may need to know whether a genomic test was done as part of a clinical diagnostic and treatment plan or as part of a college genomics donation drive. Other important contextual information about a genomic test might include the type of analysis used, clinical protocol, interpretation of the results, whether test results were routed to a pathologist for review, and how results were delivered. Provenance information can enhance the usability of genomic test results while also ensuring the privacy of such sensitive information. As a start, NMDP has been leading the development of an implementation guide for HML to FHIR, which includes provenance and device information which may serve as a reference for future iterations of the FHIR Clinical Genomics specification.

Data Storage and Management

As genomic testing becomes more sophisticated, the amount of data produced by genomic tests may continue to increase. The ability to store complex and large amounts of data is beyond the storage capabilities for most health information systems in clinical environments and often results in genomic data being stored in an external system. Beyond the challenge of large datasets, issues regarding the management of these data need to be addressed.

[25] https://www.genomeweb.com/epigenetics-research/schizophrenia-risk-snps-enriched-parts-genome-recent-methylation-changes#.XO_wHaQpCHs.

For example, a health information system may archive clinical records at a given time interval. However, because genomic data tend to be the same throughout the lifetime of a patient, the issue of how long to store data, where to store it, and how to link it to a clinical record becomes more complicated.

Health information systems that do not have the capability to request genomic data from third-party entities, such as a data repository, compound issues of accessing large data files. For example, as part of the Phase 2 pilot findings, some organizations realized their clinical information system could not access the full range of genomic results for a given test because the structured reports that providers received focused only on genomic variants. Providing the functionality to access an entire set of results is further complicated by the need to differentiate between the regions of a genome that were *intended* to be assayed compared to the regions of the genome that were *actually* assayed, which is information that may come to light after the test was performed. As the practice of incorporating genomic data at the point-of-care becomes routine, there will likely be additional complexities that will need to be accounted for and managed.

Educational Support for Providers and Patients

The power of genomic testing is generally recognized as an influential and potentially impactful part of treatment for diseases. However, many providers unfamiliar with the complexities of genomics are unclear or do not feel confident interpreting genomic test results[26] or relaying this information to their patients. Patients and caregivers also need assistance in making sense out of complex genomic tests. Supporting the development of the patient-provider relationship with educational training for providers and patient access to resources will help them work together to make the informed decisions that best fit with the patient's interest and well-being. This is also a critical step to fully integrating genomics into the care continuum.

Some Health Information Systems Are Not Designed to Accommodate Genomic Use Cases

Common genomic concepts can be difficult to represent in health information systems, such as EHRs. For example, a common genomic use case may require representation of the differences between the genomic sequences of a mother and a fetus. The mother's genomic results can be captured in her clinical record, but a fetus likely would not have a record until birth. Therefore, the issue of capturing these data as separate but linked is difficult. These issues become even more challenging if genomic tests are performed over time for subsequent pregnancies because the system must differentiate subsequent fetuses from a previous (or current, in the case of multiples) pregnancy.

Implementation of FHIR

Readiness to adopt the FHIR standard for genomic use cases among health IT developers, in clinical and laboratory industries, represented a significant challenge for the Phase 2 participants. Although there have been increases in adoption of FHIR among health IT developers, in general, this functionality is not widely available in production systems. In other cases, health IT developers are testing or are implementing an earlier version of FHIR, while the FHIR Clinical Genomics specification leverages FHIR R4. This lag in adoption of standards like FHIR makes it difficult to develop system-wide strategies if one or more of the systems producing, consuming, validating, or testing the data is not using the same or a compatible standard.

Cost and Business Drivers

Beyond the cost of genomic testing, which is decreasing, the cost of integrating genomic data into existing health information systems can often be a challenge for organizations managing multiple priorities. The cost and

[26] Williams JL, Rahm AK, Stuckey H, Green J, Feldman L, Zallen DT, Bonhag M, Segal MM, Fan AL, Williams MS. 2016, "Enhancing Genomic Laboratory Reports: A Qualitative Analysis of Provider Review," Am J Med Genet Part A 9999A:1–8 2016. [Online]. Available: https://pdfs.semanticscholar.org/4a38/4afa019ef001b84f5a73af7977c9e255260f.pdf.

resources necessary to modify, create, and support those external systems specifically for genomic data can be prohibitive for many healthcare organizations. While many clinical and research systems are moving in the direction of genomic data integration, it is still a relatively new business area. To keep pace with the advances of science and medicine, organizations should identify areas of alignment where genomics can support current business priorities. For example, the adoption of standards like FHIR could support an organizational priority to facilitate appropriate data exchange which, in turn, can support the ability to make genomic data available at the point-of-care and for research.

LESSONS LEARNED

Scaling and Scope

Appropriately determining the scope and scale of each pilot project was critical to ensure achievable goals and demonstrate applicability of FHIR to genomic use cases and the potential to scale this work at the enterprise level. This is particularly important for innovative projects that are the first of their kind, paving the way for future efforts. Demonstrating tangible progress is critical. Therefore, projects that are on short timeframes, as was the case for Phase 2, must have a clear-cut scope with a plan for future work. One tactic for laying this path is to identify and engage relevant stakeholders whose participation and buy-in is critical to the eventual implementation of an enterprise-level integration during the pilot phase. Enterprise-level integrations require the alignment of clinical and laboratory information systems, end users (e.g., providers), and administration (e.g., Chief Medical Officer). Engagement of these stakeholders, even at a cursory level, is important during the pilot phase as this presents an opportunity to discuss long-term strategy and identify potential barriers to the future enterprise-level implementation.

Knowledge of Both FHIR and Clinical Genomics

The individuals instrumental in executing the pilot project, such as implementers, had varying levels of familiarity with FHIR, which affected each organization's ability to accurately determine the level of resources and time needed to complete their pilot project. Conversely, organizations noted that if an implementer was well-versed in FHIR, it was unlikely they were equally well-versed in the nuances of clinical genomics, making it more difficult to implement FHIR for this particular clinical domain. The Phase 2 pilot project teams found that attending an HL7 FHIR Connectathon as an observer for the first time was valuable in preparing them for their participation in future Connectathons. This experience also supported their understanding of the standards development process and during the second Connectathon, gave them the dedicated time to work on their organization's pilot projects in an environment where they had access to various subject matter experts.

Health IT Developer Support of FHIR

The lag of FHIR support by health IT developers increased the time and resources needed to accomplish the pilot project objectives, as data from healthcare organizations and laboratories needed to be mapped to the FHIR specification. Some of the organizations set up their own testing environments to complete the exchange portions of their pilot project. For pilot sites whose health IT developer was FHIR-enabled, the capability was generally limited to only FHIR resources deemed more "mature" (i.e., supported FHIR DSTU 2), which did not include the information necessary for clinical genomics (i.e., FHIR R3 and R4). While tools such as ClinFHIR exist, tools that can convert test results from a laboratory into FHIR may be helpful. Further collaboration with standards development organizations, like HL7, to develop open source tooling and education to assist in implementing standards could yield more consistent and potentially quicker implementations of FHIR.

Conclusion

There were a number of successes that Phase 2 achieved in making progress toward the realization of making genomic data available for care delivery. Phase 2 successfully curated time and activities that supported the

participating organizations' ability to work on their pilot projects. These organizations found valuable resources in each other for problem solving and discussing project-related issues as well as issues related to the genomic industry in general. Project activities resulted in detailed and actionable feedback for the standards organization. The project resulted in a variety of resources, lessons learned, and artifacts that can be used as sample guidance for other organizations that are interested in implementing the use of genomic data at the point-of-care. The organizations that participated in Phase 2 actively learned about and participated in the standards development process, which relies on the greater health IT community for expertise and support. Finally, each pilot site was successful in demonstrating the exchange of genomic data and developing their proof of concepts that demonstrate the potential use of genomic data for the provision of care and eventually for research. These types of demonstrations help develop health IT that can support the goals of the Precision Medicine Initiative and 21st Century Cures Act.

APPENDIX A – CONNECTATHON FILES

The table below represents the pilot sites' sample file information and links that were used at the HL7 FHIR Connectathon. These files can also be found on the HL7 Connectathon Wiki.[27]

Table A1. Connectathon Files

Connectathon Participant	Type of GDR	XML Examples	Artifacts Link
NMDP	Master HL7 genetic variant reporting panel	Collection and Transaction Bundles of Deidentified FHIR-HLA-ABC: • FHIR-HLA-ABC-deidentified-collection • FHIR-HLA-ABC-deidentified-transaction	http://wiki.hl7.org/index.php?title=File:NMDP_Original_and_Final_Files.zip
Utah Newborn Screening Program	Newborn screening panel	Transaction Bundles of individual test results: • Bundle_Carrier • Bundle_CF • Bundle_CF_compound_het • Bundle_CF_PKU • Bundle_Normal	http://wiki.hl7.org/index.php?title=File:Final_S4GP2_Connectathon_Utah_NBS.zip
Weill Cornell Medical Center	EXaCT1 Next Generation Sequencing	Transaction Bundle of NGS: • FHIR_Donnie_Darko_v4	http://wiki.hl7.org/index.php?title=File:Completed_Cornell_CaT_Files.zip

27 http://wiki.hl7.org/index.php?title=201901_Clinical_Genomics#Scenario_10:_Implementing_Genomics_Diagnostic_Reports

APPENDIX B – GLOSSARY OF ACRONYMS

Table B1. Glossary of Acronyms

Acronym	Definition
42 CFR Part 2	Title 42 of the Code of Federal Regulations Part 2
AMIA	American Medical Informatics Association
API	Application Programming Interface
CG	Clinical Genomics
CG WG	Clinical Genomics Work Group
CHIE	Clinical Health Information Exchange
CIC	Clinical Informatics Conference
CNV	Copy Number Variant
CPIC	Clinical Pharmacogenetics Implementation Consortium
DAM	Domain Analysis Model
DBS	Dried Blood Spot
DNA	Deoxyribonucleic Acid
DUP	Duplication
EHR	Electronic Health Record
EXaCT1	Exome Cancer Test v1.0
FHIR	Fast Healthcare Interoperability Resources
GDR	Genomic Diagnostic Report
HER2+	Human Epidermal Growth Factor Receptor 2 Positive
HIE	Health Information Exchange

Acronym	Definition
HIPAA	Health Insurance Portability and Accountability Act
HL7	Health Level Seven International
HLA	Human Leukocyte Antigens
HML	Histoimmunogenetic Markup Language
HML2 FHIR	Histoimmunogenetic Markup Language to Fast Healthcare Interoperability Resources
LVHN	Lehigh Valley Health Network
NBS	Newborn Screening
NGS	Next Generation Sequencing
NIH	National Institutes of Health
NMDP	National Marrow Donor Program
ONC	Office of the National Coordinator for Health Information Technology
PMI	Precision Medicine Initiative
STU	Standard for Trial Use
Sync for Genes Phase 2	Sync for Genes Phase 2
VCF	Variant Call Format
XML	eXtensible Markup Language

APPENDIX C – GLOSSARY OF TERMS

Table C1. Glossary of Terms

Term	Definition
21st Century Cures Act[28]	The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring innovations and advances to patients who need them faster and more efficiently.
All of Us Research Program (All of Us)[29]	The *All of Us* Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health.
Application Programming Interface (API)[30]	Refers to technology that allows one software program to access the services provided by another software program.
Health IT Developer[31]	A developer builds and creates software and applications. He or she writes, debugs, and executes the source code of a software application.
Dried Blood Spot[32]	Dried blood spot testing (DBS) is a form of biosampling where blood samples are blotted and dried on filter paper.
Electronic Health Record (EHR)[33]	A digital version of a patient's paper chart that is a real-time, patient-centered record that makes information available instantly and securely to authorized users.
Exome Cancer Test v1.0 (EXaCT1)[34]	Whole Exome Sequencing by Next Generation Sequencing that takes an unbiased, exploratory look at more than 22,000 genes in both healthy and malignant cells, allowing molecular pathologists to find alterations in the cancer-development process in unexpected regions of the exome.
Fast Healthcare Interoperability Resources (FHIR)[35]	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.
FHIR Resource[36]	A resource is an entity that: • has a known identity (a URL) by which it can be addressed • identifies itself as one of the types of resource defined in this specification • contains a set of structured data items as described by the definition of the resource type • has an identified version that changes if the contents of the resource change

[28] https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf
[29] https://allofus.nih.gov/
[30] https://www.healthit.gov/sites/default/files/facas/HITJC_APITF_Recommendations.pdf
[31] https://www.techopedia.com/definition/17095/developer
[32] https://en.wikipedia.org/wiki/Dried_blood_spot
[33] https://www.healthit.gov/faq/what-electronic-health-record-ehr
[34] https://pathology.weill.cornell.edu/clinical-services/molecular-and-genomic-pathology/clinical-genomics-laboratory/exact-1-whole-exome
[35] https://www.hl7.org/fhir/overview.html
[36] http://hl7.org/fhir/resource.html

Term	Definition
Health Insurance Portability and Accountability Act (HIPAA)[37]	To improve the efficiency and effectiveness of the health care system, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Public Law 104-191, included Administrative Simplification provisions that required HHS to adopt national standards for electronic health care transactions and code sets, unique health identifiers, and security. At the same time, Congress recognized that advances in electronic technology could erode the privacy of health information. Consequently, Congress incorporated into HIPAA provisions that mandated the adoption of Federal privacy protections for individually identifiable health information.
Health Level Seven International (HL7)[38]	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.
HLA Genotyping[39]	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. Your immune system uses these markers to recognize which cells belong in your body and which do not.
Human Epidermal Growth Factor Receptor 2 (HER2/neu)[40]	A protein involved in normal cell growth. HER2/neu may be made in larger than normal amounts by some types of cancer cells, including breast, ovarian, bladder, pancreatic, and stomach cancers. This may cause cancer cells to grow more quickly and spread to other parts of the body. Checking the amount of HER2/neu on some types of cancer cells may help plan treatment. Also called c-erbB-2, HER2, human EGF receptor 2, and human epidermal growth factor receptor 2.
Human Leukocyte Antigens (HLA)[41]	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.
Implementer[42]	An implementer integrates an implementation of a standard specification through the development of software and its integration into the workflow of an organizational structure or an individual end-user.

[37] https://www.hhs.gov/hipaa/for-professionals/index.html
[38] https://www.hl7.org/about/index.cfm?ref=nav
[39] https://bethematch.org/transplant-basics/matching-patients-with-donors/how-donors-and-patients-are-matched/hla-basics/
[40] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/her2-neu
[41] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/human-leukocyte-antigen
[42] https://en.wikipedia.org/wiki/Product_software_implementation_method

Term	Definition
Interoperability[43]	According to section 4003 of the 21st Century Cures Act, the term "interoperability," with respect to health information technology, means such health information technology that "(A) enables the secure exchange of electronic health information with, and use of electronic health information from, other health information technology without special effort on the part of the user; (B) allows for complete access, exchange, and use of all electronically accessible health information for authorized use under applicable State or Federal law; and (C) does not constitute information blocking as defined in section 3022(a)." There are two types of interoperability: semantic interoperability is achieved when two systems agree on a common meaning of data, and syntactic interoperability is achieved when two systems agree on a common format for data exchange.
Modeler[44]	A modeler documents a representation of concepts and the relationships, constraints, rules, and operations to specify data semantics for a chosen domain of discourse.
Next Generation Sequencing (NGS)[45]	Next generation sequencing (NGS) is defined as technology allowing one to determine in a single experiment the sequence of a DNA molecule(s) with total size significantly larger than 1 million base pairs (1millionbp or 1Mb).
Precision Medicine Initiative (PMI)[46]	An initiative launched in 2015 that will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide providers with new tools, knowledge, and therapies to select which treatments will work best for which patients.
Specification[47]	A specification is an explicit set of requirements to be satisfied by a material, product, system, or service.
Title 42 of the Code of Federal Regulations Part 2 (42 CFR Part 2)[48]	Regulates confidentiality regarding all records relating to the identity, diagnosis, prognosis, or treatment of any patient in a substance abuse program that is conducted, regulated, or directly or indirectly assisted by any department or agency of the United States.

[43] https://www.healthit.gov/topic/interoperability
[44] https://en.wikipedia.org/wiki/Information_model
[45] https://www.sciencedirect.com/topics/medicine-and-dentistry/next-generation-sequencing
[46] https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative
[47] https://www.astm.org/FormStyle_for_ASTM_STDS.html
[48] https://www.govinfo.gov/content/pkg/CFR-2017-title42-vol1/xml/CFR-2017-title42-vol1-part2.xml