Clinical Genomics Track Summary (Discussion/Notes below)

The Montreal CG track is interested in furthering the usage of the FHIR specification on two fronts in the Genomics space, as described in the track page and the HL7 Clinical Genomics Domain Analysis Model. This was done both by implementing feedback from reports generated by early adopters and implementers of the Genomics Reporting IG into actionable tracker items and impactful examples, and by exploring complex query Operations for genomics results stored in an external GACS (Genomics Archive and Communication System)--much like how a PACS system is for imaging, but for genomics.

Participants:

Boston Children's Hospital/Harvard Medical School, MITRE, CIBMTR/NMDP, Philips, MOLIT

Notable Achievements:

- A data element and terminology gap analysis between mCODE (minimal Common Oncology Data Elements) and the current build of the CG Genomics Reporting IG was completed. This resulted in porting and validating FHIR examples for genetic variants to the CG obs-variant profile. Examples were validated against the Open FHIR Endpoint https://api-v8-r4.hspconsortium.org/CGTest/open/ populated with the structure definitions of the IG using HSPC's new Profiles module.
- Philips' panel-based molecular genomics report was also converted to an R4 CG-IG compliant bundle, leveraging DiagnosticReport-Genomics, Patient, Practitioner, Specimen, Observation-GeneticFinding, Observation-SomaticPredictiveImplication, and additional Observations for Tumor Mutational Burden (TMB), Microsatellite Instability (MSI). A corresponding example report bundle is currently available in the somatic reporting section of IG.
- Continuing work recently featured in the HL7 Newsletter, GACS Query Operations were explored by remote participants, using a Patient ID, Genomic reference sequence and arbitrary integer range Region as parameters, returning an IG-compliant Bundle of all variants found in the region and a summary of any uncallable areas, generated from VCF files (in this case, de-identified examples from the 1000 Genomes project).

Discovered Issues/Questions

- Work with mCODE/MITRE provided feedback for aligning overlapping components in Variant, clarifying guidance for Observation.method in Variant and Haplotype genomic Observation profiles, and usage of fields within DiagnosticReport's genomics profile, culminating in 3 GForge tracker items.

- Philips work uncovered missing guidance in IG for sending TMB/MSI information and relevant codings.
- Significant refactoring found to be required after analyzing existing LOINC and SNOMED-CT terminology upload implementations in hapi-fhir code towards adding terminology upload support for HLA nomenclature CodeSystems.
- When querying GACS VCF resources not aligned to PharmCAT VCF requirements, wildtype calls may not be reported, so potentially uncallable regions may be missed. Additionally, Genomic build isn't sufficient for arbitrary range querying, so specifying a reference sequence and fixed coordinate system--of '0 start, half open'--is required.

Next Steps

- Examples for the remaining use cases in the CG Domain Analysis Model will be included in the IG, including Philips' WES molecular genomics reports, clinical trial matching results reports, and others. Additional GACS query parameters supporting these use cases will be probed with test servers.
- A walkthrough of the mCODE gap analysis and IG genomics-related profiles will be prototyped and presented during the CGWG Wednesday Q2 session.
- A new branch of hapi-fhir code will be created for HLA nomenclature integration work.
- An additional region-studied profile will be drafted and proposed to deal with describing the potentially hundreds to thousands of genomic subregions that are uncallable.

Feedback and Comments, Ideas from Genomics Connectathon 21 Montreal

May 04 2019

Contributor initials:

- MK = Mark Kramer, MITRE, mkramer@mitre.org
- PW = Patrick Werner, MOLIT Institute, patrick.werner@molit.eu
- MLT = May Terry, MITRE, mayt@mitre.org
- JJ = Jamie Jones, BCH, james.jones.bch@gmail.com
- AM = Alexander Mankovich, Philips, alex.mankovich@philips.com

General comments:

- MK -- Avoid using LOINC Answer lists? The norm is LOINC for questions, SNOMED for answers

    - PW: We can't use SNOMED as it isn't free. If we need to use LOINC answer lists everywhere can be discussed.
- MK -- Avoid all the MustSupports -- not everyone who implements the Genomics IG will be willing or able to support everything. I suggest that the Must Supports be applied only at the level of a specific use case.
    - PW: i think we need some must support elements to ensure interoperability, but feedback on must-support elements which are causing problems are welcome
- MLT: Must-support requirements place a burden on EHR implementers whose use case might not need many of these attributes (obsHaplotype, obs-inh-dis-path).

- Cecil Lynch - Accenture strong need for knowledge artifacts for pharma use cases

Genomics report Profile

- MLT: code references the LOINC xcode for Master Genetics Variant Panel (81247-9) which splits up the types of panel variants. How well does this align with the current FHIR IG implementation?
    - MLT: should cardinality of dr-relatedArtifact be 0..*? There is only support for one supporting citation. Or is the implication that this is the link to the actual report and any other citations are in dr-supportingInfo?
        - JJ: yes PW and I think this is an error
- MLT: found a FHIR validation error related to the resolve() method on DiagnosticReport.result. Created GForge Issue# 21296.

Obs-variant Profile

- MK - Suggest the code for this observation should be 69548-6, not TBD-Described
- MK - mCODE has one component that is not in obs-variant, DNA sequence variation identifier, with code LOINC 48003-8 with values from https://www.ncbi.nlm.nih.gov/clinvar (extensible).
    - Need to file tracker for re-combining complex variant components
- MK - Suggest that "Method" should not have a required binding, because new methods come along all the time. At best, extensible. For cancer-related genetic tests, we use codes from NCI Thesaurus (MLT: opened GForge Issue 21283):

```
ValueSet:       GeneticTestMethodVS
Description:    "The method used to perform a genetic test, drawn from NCI
Thesaurus. Examples include Fluorescent in situ hybridization (FISH), polymerase
chain reaction-based assays (PCR), and next-generation sequencing (NGS).

NCIT#C130179       'Allele Specific Primer Polymerase Chain Reaction'
NCIT#C18084        'Comparative Genomic Hybridization'
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NCIT#C19641 'Dideoxy Chain Termination DNA Sequencing'
NCIT#C63328 'DNA Methylation Analysis'
NCIT#C17563 'Fluorescence In Situ Hybridization'
NCIT#C16768 'Karyotyping'
NCIT#C18477 'Microarray Analysis'
NCIT#C139286 'Microsatellite Stability Assessment'
NCIT#C116161 'Multiplex Ligation-dependent Probe Amplification'
NCIT#C101293 'Next Generation Sequencing'
NCIT#C17003 'Polymerase Chain Reaction'
NCIT#C51962 'Real Time PCR'
NCIT#C17093 'Restriction Fragment Length Polymorphism'
NCIT#C18136 'Reverse Transcriptase-Polymerase Chain Reaction'
NCIT#C18473 'RNA Analysis'
NCIT#C17565 'Sequence Analysis'
NCIT#C116151 'Single Nucleotide Polymorphism Array'
NCIT#C16356 'Southern Blotting' "

- MK -- mCode use the following two value sets across several profiles -- Let's coordinate! (SCT = SNOMED-CT)
    - ValueSet: DetectedNotDetectedVS
    - Description: "Value set consisting of the answers Detected (Present) and NotDetected (Absent). The terms detected and not detected are preferred because they reflect outcomes of experimental observation, while present and absent suggest ground truth. This value set reconciles or combines LOINC answer lists LL956-4, LL750-1, LL744-4, LL955-6, LL3950-4, LL3250-9, LL2872-1, LL2410-0, LL2355-7."
    - SCT#260373001 "Detected"
    - SCT#260415000 "Not detected"
    - SCT#42425007 "Equivocal. Equivocal represents a borderline value, too close to call; for example, a value very close to a cut-off between positive and negative."
    - SCT#82334004 "Indeterminate. Indeterminate means the results were uninterpretable, or cannot be determined; technical issues prevented obtaining a valid result."

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    - ValueSet: PositiveNegativeVS
    - Description: "Interpretation of a test result as positive, negative, equivocal, or indeterminate. Consolidates LOINC answer lists LL360-9, LL2329-2, LL2038-9, LL2021-5, LL2010-8, LL2009-0."
    - SCT#10828004 "Positive" //LA6576-8
    - SCT#260385009 "Negative" //LA6577-6
    - SCT#42425007 "Equivocal. Equivocal represents a borderline value, too close to call; for example, a value very close to a cut-off between positive and negative"
    - SCT#82334004 "Indeterminate. Indeterminate means the results were uninterpretable, or cannot be determined; technical issues prevented obtaining a valid result."

Need 'mixed' on loinc https://r.details.loinc.org/AnswerList/LL378-1.html list may need work…

Want Observation.specimen to be 0..* normative Observation is 0..1

Validation of fields that require a list (even though it appears to be 0..1 or 1..1 it may have been constrained in the profile from a 0..* or 1..* and still must be given as a list)

JJ: Oncology example: DiagnosticReport.performer as practitioner error (and not organization)
We are incorrectly constraining in our Genomics Report profile

JJ: Links to previous work converting reports into FHIR DSTU2 (from Gil/Jeremy Warner and students):

- https://etd.library.vanderbilt.edu/available/etd-03252016-111331/unrestricted/Rioth.pdf
- https://github.com/lifeomic/foundation-xml-fhir/blob/master/test/convert_tests.py
- https://www.healthit.gov/sites/default/files/sync_for_genes_report_november_2017.pdf

obs-haplotype Profile

MLT: Specimen is a required element. Should this be optional? Update: Known issue: GForge Issue #19920 opened by BobD.

May 05 - reporting and next steps

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Participant: MITRE (May Terry, Mark Kramer)

Track Goal: To better align the genomics elements from the minimal Common Oncology Data Elements (mCODE) with the current build of the CG Genomics Reporting IG.

Notable Achievements:

- Completed a data element and terminology gap analysis of mCODE genomics specific profiles with CG Genomics Reporting.
- Provided feedback for improving obs-variant, DiagnosticReport, and haplotype profiles; opened one GForge tracker related to obs-variant method.
- Ported FHIR example for genetic variant to the CG obs-variant equivalent profile and successfully validated the ported example.
- Uncovered validation errors related to slicing on DiagnosticReport.result not being supported; Created GForge Issue# 21296.

Next Steps:

- Present a walkthrough of the mCODE IG genomics-related profiles and the gap analysis during the CGWG Wednesday Q2 session.
- Prototype a new version of mCODE genomics-related profiles that are based on the FHIR R4 CG Genomics Reporting IG.

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Participant: Philips (Alex Mankovich)

Track Goal: Convert production data model to R4 and IG compliant resources

Notable Achievements: Converted panel-based molecular genomics report to R4 and IG compliant bundle

- DiagnosticReport-Genomics, Patient, Practitioner, Specimen, Observation-GeneticFinding, Observation-SomaticPredictiveImplication, and additional profiles for Tumor Mutational Burden (TMB), Microsatellite Instability (MSI).
- Full transaction bundle added to somatic reporting section of IG

Next Steps:

- Work to include support for TMB/MSI in IG is needed
- Convert WES molecular genomics report to R4 and IG compliant bundle
- Integrate panel target and coverage information and model as Observation-RegionStudied

- Integrate clinical trial matching results into appropriate resource (ResearchStudy?)

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Participant: CIBMTR/NMDP (Joel Schneider)

Track Goal: add terminology upload support for HLA nomenclature CodeSystem to hapi-fhir

Notable Achievements:

- Analyzed existing LOINC and SNOMED-CT terminology upload implementations in hapi-fhir code.
- Discussed options for adding new CodeSystem upload support to hapi-fhir with James Agnew, leading toward a decision that the best option is to add imgthla terminology upload support directly to the hapi-fhir code.
- Began process of refactoring old code for generating HLA nomenclature CodeSystem bundle to integrate with hapi-fhir terminology upload framework.

Next Steps:

- Create new hapi-fhir code branch (based on hapi-fhir master branch) for continuation of this work.
- Develop, test, and debug.

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