FHIR Subgroup Meetings 5/18/20 - 9/14/20

Quick link to this sign-in/notes document: http://tinyurl.com/fhirgenomics

Zulip CG discussion: https://chat.fhir.org/#narrow/stream/179197-genomics

Schedule
May 18 - Connectathon wrap-up & Next steps
May 25 - X - memorial day
June 1 - JIRA review
June 8 - open questions for next cycle
June 15 - DEVDAYS
June 22 - functional annotations
June 29 - X
July 6 - review examples
July 13 - prep for block vote 7/21
July 20 - Connectathon 25 discussion
July 27 - Region studied
August 3 - IG development planning, tracker reviews
August 10 - X
August 17 - WGM planning
August 24 - Example identification, pulled trackers
August 31 - tracker review
September 7 - X - labor day
September 14 - (WGM prep) - variant consequence recap
FHIR Subgroup Meeting September 14th, 2020

We are ZOOMing away from FCC. New coordinates:

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Sign In: (presiding co-chair - Jamie Jones)

1. Arthur Hermann - Kaiser Permanente - arthur.hermann@kp.org
2. Anand Kulanthaivel - Clinical Architecture - anand_kulanthaivel@clinicalarchitecture.com
3. Hayden Bader - Epic - hbader@epic.com
4. Kevin Power - Cerner - kpower@cerner.com
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7. Bob Dolin - Elimu Informatics - bdolin@elimu.io
8. Liz Amos - NLM - liz.amos@nih.gov
9. May Terry - MITRE - mayT@mitre.org
10. Lloyd McKenzie - Gevity - lmckenzie@gevityinc.com
11. Bob Milius - NMDP/CIBMTR - bmilius@nmdp.org (joined at 10:34am)
12. Rachel Kutner - Epic - rkutner@epic.com
13. 

Agenda:

1. Connectathon recap - open floor
2. Variant Consequence (Liz)
3. Other trackers

Discussion:

1. Variant Consequence (Liz)
   a. To convene with Rachel on background for proposals here
      i. Term definitions and context
         1. 2 concepts (functional effect and molecular consequence)
      ii. Concern: amino acid change type is a subset of molecular consequence terms -- (how) should we resolve this overlap?
         1. Is the smaller-scoped term worth keeping? (in LOINC? In our IG?)
2. Could change the name or define as a new concept
   a. Ncbi molecular consequence definition
      i. Ncbi list
      ii. Also allow any items from the SO term for structural consequence
   iii. Functional effect concept may need more thought -some terms are very complex to derive/assume
      1. Less guidance on functional effect - requires more evidence/etc
      2. Lab computes and provides these
      3. Used to predict pathogenicity/etc
      4. Potentially able to filter patients for clinical trial eligibility
   iv. Concern over splitting primary data from derived/inferred data
      1. Molecular consequence can be reliably computed from a specific source
   v. Thoughts on how the user interacts with these differently, if at all?
      1. Receiver may ignore annotations and re-derive them (especially older/proprietary annotation)

2. Connectathon recap
3. Other trackers
   a. https://docs.google.com/spreadsheets/d/1aqoEa7HqDXwCGspN1pYCiImVRFQRaOK-lgJK6Hfxagzl/edit#gid=0

FHIR Subgroup Meeting August 31th, 2020

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7. Daniel Rutz - Epic - drutz@epic.com
8. Rachel Kutner - Epic - rkutner@epic.com
9. May Terry - MITRE - mayT@mitre.org
10.

Agenda

1. Other JIRAs needing resolution:
2. New ones to log before WGM?

Discussion

1. Current list of pending JIRA:
   a. [Link](https://docs.google.com/spreadsheets/d/1aqoEa7HqDXwCGspN1pYCimVRFQraOK-IgJK6Hfxagzl/edit#gid=0)
   b. JIRA filter: project = "FHIR Specification Feedback" AND (Specification = "Genomics Reporting (FHIR) [FHIR-genomics-reporting]" OR "Work Group" = "Clinical Genomics [cg]") ORDER BY created DESC
   c. Variant components:
      i. Molecular consequence / functional effect
         1. Liz making us some slides
      ii.
   2. Others to log?
      a. Component grouping on variant
      b. Example guidance cleanup -
      c.
FHIR Subgroup Meeting August 24th, 2020

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20. Lloyd McKenzie - Gevity - lmckenzie@gevityinc.com
21. Ling teng - BWH - tenglingling@gmail.com

Agenda:

1. Pulled trackers
2. Examples for WGM sessions

Discussion:

1. Uncallable sub-regions
   a. Moving new concept to component rather than value
   b. Question on extension vs component?
      i. 80% vs 20%
   c. Examples needed using this component
      i. More reports presenting uncallable regions?
      ii. Granularity on info here vs in test description
      iii. Clinicians/research clinicians needing this information?
         1. Meaningful denominator for population studies on variant databases
         2. Calculating wildtypes / reference calls
         3. Determining follow-up tests?
4.

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<th>FHIR-25296</th>
<th>Uncallable subregions in a region studied</th>
<th>Bob Dolin</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>To allow full use of the current profile's components, add a new component [0..1] for region-studied with a new code for describing callability of a region. Its value is an extensible binding to a local answer list with the 3 LOINC answer codes:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Callable tbd-callable</td>
</tr>
</tbody>
</table>

Add in textual guidance for this component, along the lines of:

'The absence of this element needs guidance

From LOINC: new code for callability of a region studied, value set including a new code answer: “called”

Callable | uncallable - pertains to test characteristic over the region

2. **Examples for WGM sessions**
   a. **Build something out akin to Associated Phenotype Example Modeling**
      i. Text Extensions from eMERGE
      ii. Failed test - not enough tumor sample/etc
      iii. Multiple representations of a variant? Bret had some from last connectathon
      iv. V2 examples

3. **Removing variant components (didn’t cover)**
   a. **Split off into multiple trackers:**
      i. db-SNP: needs special treatment--clean guidance and an invariant with alt
      ii. Complex variant type: support removing, needs examples for how to use with other structures:
      iii. Copy number / arrCGH
         1. Update datatype of copy number to include decimals?
         2. Do we keep an ordinal copy number type field as well?
            a. Receivers can calculate this from copy number if present
            b. Senders can use concepts in SO under dna-chg-type
FHIR Subgroup Meeting August 17th, 2020

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12. Rachel Kutner - Epic - r kutner@epic.com
13. Clem McDonald - NLM - clemmcdonald@mail.nih.gov
14. Ling teng -BWH-tenglingling@gmail.com

Agenda:

3. Tomorrow’s block vote
   a. https://jira.hl7.org/browse/FHIR-27146?filter=12310&qjql=project%20%3D%20%22FHIR%20Specification%20Feedback%22%20AND%20(Specification%20%3D%20%22Genomics%20Reporting%20(FHIR)%20%5BFHIR-genomics-reporting%5D%22%20OR%20%22Work%20Group%20%3D%20%22Clinical%20Genomics%20%5Bcg%5D%22)%20AND%20grouping%20%3D%20Ready-For-Vote%20%20ORDER%20BY%20created%20DESC
   b. Compound het??
4. WGM topics
   a. https://confluence.hl7.org/display/CGW/2020-09+CG+WGM+Agenda+-+Virtual
5. Other JIRA:
Discussion:

1. Block vote
   a. Leave component jira in or pull out?!
   b. Complex variant type
      i. Bob D: suggest still leaving jira in (and taking complex variant type component out)
         1. Related to variant vs allele conversation:
            a. Example1: ref A, alt G, state = heterozygous - this doesn’t imply that the patient is A/G - doesn’t specify what’s happening on the other chromosome - need another obs for that
            b. ‘Compound heterozygous’ often implies changes on each chromosome at separate positions
            c. ‘Double heterozygous’ may cover the 2 alts at the same position case - but clinicians may use this differently
            d. Example2: ref A, alt G,G
      ii. Rachel: labs tend to send info separate for compound het if phase is unknown - sending as much info as they have and options for follow-up testing (including a narrative). Some labs use / to separate if it is known.
         1. Support removing component in its current state, considering alternative representation
   c. WILD TYPES
      i. Bob M: should discourage sending this term -
      ii. This is explicit in GA4GH VR spec - which is a highly customized format that requires allelic info in addition to variants
      iii. Heterozygous generally infers the other homolog is wild type. (is this recorded anywhere in our IG?) see FHIR-27137
   d. Db-SNP concern on variation code - increase cardinality on code??
      i. With 0..1 one could still send multiple codings
      ii. One code: loinc 81252-9, a clinvar code, a db-snp code, etc.
      iii. GROUP OK WITH THIS (mostly)
   e. Copy number
      i. Actual copy number (and arrcgh, either integer or decimal) sometimes hard to get in real world reports
      ii. Ordinality (gain / loss)
      iii. One place to hold relevant information on copy number (method agnostic) would be ideal - currently we would only have a Count type
      iv. Patrick after the buzzer: Reconsider guidance on dna-chg-type (contains copy-number-gain/loss)
Chat

● From Patrick Werner to Everyone: (10:02 AM)
  ○ https://docs.google.com/document/d/1FGCQRtxJKyHhnC1uB_t4sJZ9yXbLMGOqP
  XHPr5tSLLQ/edit#heading=h.eh5jej8vvoqk can see it without being signed into
  confluence, weird.
● From Arthur Hermann to Everyone: (10:19 AM)
  ○ Wondering if we are in alignment with GA4GH Variant Profile?
    https://vr-spec.readthedocs.io/en/1.0/ - or if their definition helps us get clearer
● From Patrick Werner to Everyone: (10:47 AM)
  ○ don’t want to waste time on the call, but i agree. We have a to create a structured
    representation of LOINC terms which are needing changes and concepts we need a
    loinc code for.
● From Rachel Kutner (Epic) to Everyone: (10:53 AM)
  ○ Can we pull the CNV fields out of the tracker and have a separate tracker for better
    supporting CN

FHIR Subgroup Meeting August 3th, 2020

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4. Kevin Power - Cerner - kpower@cerner.com (:09 after the hour)
5. May Terry - MITRE - mayT/mitre.org
6. Bob Dolin - Elimu Informatics - bdolin@elimu.io
7. Michelle Barry-Availity michelle.barry@availity.com
8. Ling teng -BWH-tenglingling@gmail.com

Agenda:

1. IG development planning/FHIR#27942
2. Other Trackers in progress

Discussion:

1. IG development planning/FHIR#27942
   a. Moving build of SDs to JSON in the resource folder, FHIR comments can cover xml comment functionality
      i. Zulip discussion about JSON5 (JSON with comments): Comments in JSON
      ii. the vsCode FHIR plugin can convert FHIR JSON<->XML:
   b. FSH track participation?
      i. Bob M and May will attend and attempt to draw up some of our profiles in FSH
         1. Some project files will be shared, considering a common repo
         2. Look at setting up time during WGM to recap and align on next steps.
         3. Step-by-step tutorials for tooling are available
            a. https://fshschool.org/docs/getting-started/
            b. https://fshschool.org/docs/sushi/
            c. https://fshschool.org/docs/tutorials/
   c. Other build errors - Jamie will push to a branch if Kevin can’t today
      i. Attempting to localize message opd-0: Name should be usable as an identifier for the module by machine processing applications such as code generation [name.matches('^[A-Z][A-Za-z0-9_-]{0,254}$')], but no such equivalent message exists for the local en_US
      ii. Exception in thread "main" java.lang.Error: Access single value, but value count is 0

2. Tracker progress
   a. Annotations proposal WIP on FHIR-27747 and FHIR-27748 (Rachel and Liz)
      i. Need full definitions for both terms
      ii. Example lists for LOINC submission (extensible / example bindings)
   b. Indeterminates via region-studied FHIR-25296 jamie to update proposal
      i. Group had determined to do subtraction before reporting
      ii. Uncallable regions were still "studied"
      iii. Add guidance and examples to not use Variant to convey a non-callable gene
      iv. Proposal B: allow Observation.value to convey callability
          1. “No Call different from Absent” on variant answer list
   2. Add in extensible binding to
      a. (Present LA9633-4 | No Call LA18198-4 | Unknown LA4489-6)
3. Future extensible Options for value
   a. (Callable | uncallable) | high-quality | intermediate quality
   v. Proposal C: separate profile for listing uncallable regions
   vi. Proposal A: add uncallable sub-region component
       1. Hard to convey uncallable whole genes

c. Diagnostic Report code FHIR-27864
   i. define a ValueSet based on a LOINC category property that we could use to
      bind to GenomicsReport(DiagnosticReport).code

FHIR Subgroup Meeting July 27th, 2020

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12.

Agenda:
1. Connectathon/WGM update
2. Variant annotations: 1 component or 2?
3. Observation.value[x] on region_studied and implication profiles
Discussion:

1. Connectathon 25 - NO CG TRACK
   a. WGM attendance / timezones: https://forms.gle/iWGWsv2wfMwEsXvXA FILL OUT TODAY

2. The MISO Sequence Ontology Browser - SEQUENCE VARIANT
   a. Work ongoing - good documentation is key with whichever model we choose
   b. Value in having 2 components vs 1? Mapping to separate gui elements, could define own slicing
   c. May be different ways in annotating variant vs implication
   d. May: loose guidance in particular makes conformance difficult
   e. Bob M: one approach we have taken here is to have groups use our IG as a framework for building your own use case’s IG
   f. Bob D: would like to see HL7 IGs enable semantic normalization of data types if possible
   g. Patrick: being universal/international complicates this. Another point is that we have open slicing. Could consider strict profiles with closed slicing
   h. Liz: hoping to suggest a starter set of terms and then binding to a branch more broadly

3. Observation.value[x]
   a. http://build.fhir.org/observation.html#gr-other
   b. http://build.fhir.org/observation.html#code-interop
      i. Implication: valueString instead of Observation.note
      ii. Region-studied
         1. Currently treated like a panel (but of components, not derived/hasmember observations)
         2. Current pattern:
            a. Region studied: explicit assertions about study regions
               i. Could list explicit regions that were uncallable
               ii. Could flag whole region described by profile as uncallable
               iii. Could do subtraction up front and only report in region-studied callable regions (may need separate variable for stuff you tried to look at but couldn’t)
            b. Variant: explicit assertion of a found/not-found variant
               i.
            c. If a variant that should be in the region that was studied isn’t there in the report, should be able to calculate/assume that it wasn’t observed

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<td></td>
<td>Uncallable subregions in a region studied</td>
<td>Bob Dolin</td>
<td>Not able to easily report large uncallable regions (something commonly seen on reports)</td>
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### Able to be computed directly from BAM

Use case: pharmcat star allele calling (requires SNPs and wild types)

Bob M: I like having this be one regions that were (fully) studied. Example is KIR genes-lots of structural variants, we often just report whether it’s there or not

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<th>FHIR-24598</th>
<th>How to reference a region studied observation from genotype, haplotype, variant observations</th>
<th>Bob Milius</th>
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<td>region studied</td>
<td>FHIR-20314</td>
<td>Ideal strategy for handling a large amount of genomic results. Method needed to describe what things you looked at and didn't touch.</td>
<td>Apurva Dharia</td>
</tr>
<tr>
<td>variant</td>
<td>FHIR-27137</td>
<td>Clarify the representation of wild type in variant profile</td>
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| region studied | FHIR-20314 | Ideal strategy for handling a large amount of genomic results. Method needed to describe what things you looked at and didn't touch. | Apurva Dharia |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| variant | FHIR-27137 | Clarify the representation of wild type in variant profile | Bob Dolin |
Agenda:

1. Connectathon 25 September 9-11 (track proposal deadline is tomorrow, July 21st)
   a. [https://confluence.hl7.org/display/FHIR/2020-09+Connectathon+25](https://confluence.hl7.org/display/FHIR/2020-09+Connectathon+25)
      i. Currently lists 19 tracks
      ii. Options/questions
         1. Registered
            a. v2-to-FHIR alignment
               i. Bob D: is this based on genomics LRI from 2 years ago? Know a lab using LRI looking at moving to FHIR
               ii. Kevin: much more generic initiative for tooling from all of v2. Alignment goal is to get inputs from our LRI to land in/near our IG, but seems like they are still ramping up to that with more basic functionality first. Tooling is a major focus. V2 updates (and mappings) are on our work group
            iii. **Mapping page on each of our structure definitions as a starting point**
            iv. Liz: difficulty in seeing what test was requested vs reported on in V2 panel codes.
            v. Jamie is useless in V2, May, Kevin and others may be better resources
            vi. Bob D: question is if we want to push for labs to reprocess their raw data into FHIR rather than go through V2/LRI. Hoping to invite them for their use case

2. Pending
   a. FSH?
   b. Other projects in CG space?
c. Dedicated CG track? (could be subject/problem focused rather than WG in general)
   1. Often focused on client+server interactions
   2. Validation of designs/ideas still valid
      ii. MolecularSequence
      iii. IG STU2 - expectation to test the spec should be satisfied by last connectathon
      iv. Others??

d. Planned attendants (not to a specific track)
   i. Bob M - would like to focus on MolecularSequence (and MolecularSequence.variant) would also like to look at FSH conversion
   ii. May - could split some time here with FSH representation, our IG could be a good stress test for FSH
   iii. Bob D - working on multi-region queries and uncallable subregions in find-subject-variants operation

2. Trackers carryover
   a. Region Studied (uncallable)
      i. Absence of a variant in a vcf file (what was tested vs found vs not callable)
      ii. Guidelines for inference of wildtype (sometimes possible, sometimes very dangerous)
      iii. Method for determining uncallable? Lab-defined criteria, same as other components/values
      iv. Bob M: take a look at dataAbsentReason (and O&O’s definition) Should have a narrative for this at the variant level as well

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<td>Bob Milius</td>
<td>Looking for guidance on pointing findings to regions studied</td>
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<td>Ideal strategy for handling a large amount of genomic results. Method needed to describe what things you looked at and didn't touch.</td>
<td>Apurva Dharia</td>
<td>Suggest persuasive with mod - needs more guidance on region studied</td>
</tr>
</tbody>
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b. Implications
   i. **Associated Phenotype Example Modeling**
      1. See ‘version B’ tab:
FHIR Subgroup Meeting July 13th, 2020

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26. Daniel Rutz - Epic - drutz@epic.com
27. Ling teng - BWH-tenglingling@gmail.com

Agenda:
1. Prep for block vote on recent trackers
   a. Tooling update FHIR-27942 - Convert IG from spreadsheets to StructureDefinitions
   b. Molecular consequence
   c. Region Studied

Discussion:
1. Tooling update FHIR-27942 - Convert IG from spreadsheets to StructureDefinitions
   a. Not a substantive change scoped yet - just backend tooling change to move away from spreadsheets
   b. Forge - free for non-commercial projects
      i. Not open source
c. FSH (FHIR Shorthand) has some functionality to reverse engineer FSH from SDs
   i. Concern over roundtripping
   ii. Can escape FSH syntax with ^ and write out SD syntax
   iii. Open source support is building
   iv. May and Bob M to look into migration to FSH in the future (not a tracked change)

2. Molecular Consequence

<table>
<thead>
<tr>
<th>Variant</th>
<th>FHIR-27748</th>
<th>Rename &quot;Functional Annotation&quot; Component to &quot;Variant Consequence&quot;</th>
<th>Rachel Kutner</th>
<th>7.13 support for this How does this change the structure of the sequence? (predicted) How does this change the molecular behavior?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Would point to clinvar’s molecular consequence definition and fix AA change type here too IG needs to support these concepts. Either add this branch of SO or roll up Functional Annotation to cover both.</td>
</tr>
<tr>
<td></td>
<td>FHIR-27747</td>
<td>New Component for Functional Effect</td>
<td>Rachel Kutner</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>variant</th>
<th>FHIR-27747</th>
<th>New Component for Functional Effect</th>
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<th>How does this change the molecular behavior? IG needs to support these concepts. Either add this branch of SO or roll up Functional Annotation to cover both.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>there is concern of overlap with <a href="https://loinc.org/LL380-7/">https://loinc.org/LL380-7/</a> (amino acid change type)</td>
</tr>
</tbody>
</table>

a. Is the added value of having a separate component worth the complexity? Concern over immaturity of the space and alignment with emerging GA4GH model
   i. Prop part 1
      1. Bind functional annotation to sequence_variant (parent term) and remove amino acid change type
         a. Requires terminology understanding to differentiate
      2. Create second term and properly define guidance
         a. Patrick prefers keeping separate
            i. functional effect - binding:
               SO:functional_effect_variant
            ii. variant consequence - binding: SO:structural_variant
      3. Component codes? Can/should we use SO top level terms for the codes
   ii. Prop part 2 FHIR notes 713
      1. Provide concept Map to SO from our (v2) loinc list and include in guidance for “variant consequence”

3. Mode of Inheritance

<table>
<thead>
<tr>
<th>variant (also loinc)</th>
<th>FHIR-27743</th>
<th>Update answer list for Mode of</th>
<th>Rachel Kutner</th>
<th>Change not necessary but can point to a different list as well. Binding is</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patrick: identified duplicates of the MSI concept in Loinc?: 62862-8 & 81695-9

FHIR Subgroup Meeting July 6th, 2020

We are ZOOMing away from FCC. New coordinates: https://zoom.us/j/2980068716
Find your local number: https://zoom.us/u/adNIRW2P8J
Quick link to this sign-in/notes document: tinyurl.com/fhirgenomics

Sign In: (presiding co-chair - Jamie Jones)

1. Arthur Hermann - Kaiser Permanente - arthur.hermann@kp.org
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3. May Terry - mayT@mitre.org
4. Bob Milius - NMDP/CIBMTR - bmilius@nmdp.org
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6. Michelle Barry-Availity - michelle.barry@availity.com
7. Bob Dolin - Elimu Informatics - bdolin@elimu.io
8. Peter Muiir - Peter@PjmConsultingLLC.com
9. Lloyd McKenzie - Gevity - lmckenzie@gevityinc.com
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11. Ling Teng-BWH - tengtingling@gmail.com
12. Clem McDonald - NLM - clemmcdonald@mail.nih.gov

Agenda:

1. Implication Examples
2. Region Studied
3. Molecular Consequence
4. Diagnostic Report Code list
Discussion:

1. Implication examples
   a. associated phenotype/cancer stress test
   b. Associated Phenotype Example Modeling
   c. FHIR sheets (lists components on our current Observation structures in a google sheet)
      i. Medication classes in reports? Should these be modeled in medication-assessed? Previous guidance is to just list the drug and rely on the interpreting system to go deeper. Rather than list the drug class as a separate component, may be appropriate to list as a second coding within the same component.
         1. Standardization in drug knowledgebases is difficult
      ii. Post coordination in associated cancer (context going in to the report) determines level of evidence for a lot of therapies
         1. Granularity in terms for cancer may be needed
      iii. “Responsive” vs “Presumed responsive” in medication effectiveness for therapies differing from patient’s current diagnosis (AMP Tier 2)
   d. Jamie to take a stab at a diagram and add concept definitions to spreadsheet

<table>
<thead>
<tr>
<th>Implications</th>
<th>FHIR Reference</th>
<th>Description</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>implications</td>
<td>FHIR-26945</td>
<td>clarifying 'context' vs 'risk-of' for associated phenotype and/or associated cancer component</td>
<td>Bret Heale</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-26426</td>
<td>Add new component for 'Potential Clinical Trial Match'</td>
<td>Kevin Power</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-26380</td>
<td>describe adverse effects on Implication</td>
<td>James Jones</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-26379</td>
<td>Support for detailed lab text on Implications</td>
<td>James Jones</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-25170</td>
<td>relatedArtifact extension on Observation.component</td>
<td>James Jones</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-20198</td>
<td>Medication Impact profile obs-med-impact (CG IG)</td>
<td>Larry Babb</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-19844</td>
<td>PGx High Risk Allele Medication Impact is confusing</td>
<td>Larry Babb</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-19244</td>
<td>Level of Evidence CodeableConcept should have some kind of binding</td>
<td>Patrick Werner</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-16175</td>
<td>Genetic Impact - Add ACMG reference for level of evidence</td>
<td>Kevin Power</td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-16082</td>
<td>PGx Impact - Allele functional status</td>
<td>Kevin Power</td>
</tr>
</tbody>
</table>

2. Region Studied
3. Molecular Consequence
4. Diagnostic Report Codes
FHIR Subgroup Meeting June 22nd, 2020

We are ZOOMing away from FCC. New coordinates:

https://zoom.us/j/2980068716

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3. Peter Muir - Peter@PjmConsultingLLC.com
4. Bob Milius - NMDP/CIBMTR - bmilius@nmdp.org
5. Daniel Rutz - Epic - drutz@epic.com
6. Liz Amos - NLM - liz.amos@nih.gov
7. Ning Xie - BWH - nxie1@bwh.harvard.edu
8. Hayden Bader - Epic - hbader@epic.com
9. Bob Dolin - Elimu Informatics - bdolin@elimu.io
10. May Terry - MITRE - mayT@mitre.org
11. Brooke Greenstein - Epic - bgreenst@epic.com
12. Rachel Kutner - Epic - rkutner@epic.com
13. Bret Heale - Intermountain Healthcare - bheale@gmail.com
14. 
15. 

Agenda:

1. Variant annotations
   a. Are Clinvar codes and/or Sequence Ontology terms used in your workflows?
   b. What do you think about representing ontology terms based on how they were obtained?
      i. Calculated just from position and change type (e.g. from NCBI)
      ii. Predicted from another resource (how much info here is not proprietary)
      iii. Experimentally Observed
   c. Do you feel nothing is lost if they were all lumped together (and assumed predicted by a reputable source)?
2. Other questions for the group
3. Current Reporting Profiles

Discussion:

2. Variant annotations
      i. Clem: Ncbi database of user submissions. Many attributes stored and associated with each variation code, including places for (sequence) ontology terms to help identify the thing they are talking about
      ii. Some responses obtained and shared on Zulip:
         1. Molecular and functional consequence is critical in the result interpretation. Standardization is another matter that is nice to have from the clinician standpoint, but I would think whatever labs use can be slotted in to that field so not mission critical for it to be the same nomenclature / source / formatting.
            a. Leslie Manace MD, MPhil, FACMG
            b. TPMG Regional Director | Precision Tracking
            c. Genetics | Screening & Tracking
         2. I agree with Dr. Manace that information on both molecular and functional consequence is paramount in interpretation of the results. As a matter of fact they are intertwined. Information on molecular change ( location , missense , splice site , frame shift etc ) reflects on the possible functional effect on the protein and hence the clinical consequence .
            a. For example from a report from a recent pt from a lab that we use . You can see how they list information on the variation: “CASQ2, Intron 5, c.606+1G>C (Splice donor), homozygous, Likely Pathogenic
            b. This sequence change affects a donor splice site in intron 5 of the CASQ2 gene. It is expected to disrupt RNA splicing and likely results in an absent or disrupted protein product. (MOLECULAR)
            c. This variant is not present in population databases (ExAC no frequency). (MOLECULAR)
            d. This variant has been observed in individual(s) with clinical features of catecholaminergic polymorphic ventricular tachycardia (Invitae). ClinVar contains an entry for this variant (Variation ID: 190743). (MOLECULAR)
            e. Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site, but this prediction has not been
confirmed by published transcriptional studies. (FUNCTIONAL)

f. Donor and acceptor splice site variants typically lead to a loss of protein function (PMID: 16199547), and loss-of-function variants in CASQ2 are known to be pathogenic (PMID: 12386154). (FUNCTIONAL)

g. In summary, the currently available evidence indicates that the variant is pathogenic, but additional data are needed to prove that conclusively. Therefore, this variant has been classified as Likely Pathogenic."

3. Invitae: We use Molecular Consequence Sequence Ontology (SO) terms to calculate our variant names and to aid in variant interpretation, but they are not directly used or displayed in the report data. When experimental data is available in the literature then we will also take the Functional Consequence of the variant into consideration for variant interpretation. This is captured through Sherloc evidence codes (PMID: 28492532). We do not use ClinVar data in our reporting, but do reference ClinVar Variation IDs where available for the general information of the clinician.

a. Why aren’t these reported? Is it proprietary? Or is there no good place to put it?

b. Current list for amino acid change type is limited as a concept, important effects are not captured here semantically.

c. Jamie: some of these effects are complex and may need to be derived from multiple variants, lends to a separate Observation rather than component
   i. Rachel: even for complex variants, it is calculated per variant
   ii. Bret: also an obvious trade-off here with complexity for a calculated
   iii. Jamie: sounds good, i take it back

d. Liz: need to reconcile with GA4GH effort here too, will send link

3. Current Reporting Profiles

a. Comments on labs looking mostly at V2 LRI modelling for their concepts. Group aims to accommodate translations to FHIR as much as possible. It is a much richer structure and enables a lot of progress leveraging a lot of work.
   i. Dan: Not exactly a direct comparison, and workflow patterns in FHIR are in early steps of maturation. Question of the right tool for each job.
   ii. Bret: much more granularity in IG, expands even on V2 LRI. Not all LOINC decisions that work in V2 will line up well when asking for higher granularity.
   iii.

b. Recent example of variant with 2 implications

4. Open trackers on Variant and Molecular Sequence

| Variant | FHIR-27748 | Rename "Functional Annotation" Component to "Variant Consequence" | Rachel Kutner | Loss of hetero may have been on old loinc list here, may want to simply roll this list up to its parent term |
### Variant

<table>
<thead>
<tr>
<th>FHIR-27747</th>
<th>New Component for Functional Effect</th>
<th>Rachel Kutner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request for terms similar to but not in amino acid change type list (things in utr/etc) lists are similar to clinvar's molecular consequence or VEP. Higher effects can be predicted from multiple variants (more so than from a single variant, downstream effects can be overwritten, etc) or observed (from mass spec, eg). Need a place for these,</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FHIR-27743</th>
<th>Update answer list for Mode of Inheritance LOINC code</th>
<th>Rachel Kutner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persuasive with mod Lis: will need a new code - requested</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FHIR-27146</th>
<th>Remove components from Variant Profile</th>
<th>Kevin Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggest persuasive (with mod re: alt allele on db-SNP) Confirm (w/ clinvar etc) that compound heterozygous has a home or appropriate way to communicate - may be more appropriate as tied to the phenotype than the variants themselves [<a href="https://www.ncbi.nlm.nih.gov/clinvar?term=(%22Compound%20heterozygote%22%20AND%20(%22haplotype%22%5BComplexity%5D))">https://www.ncbi.nlm.nih.gov/clinvar?term=(%22Compound%20heterozygote%22%20AND%20(%22haplotype%22%5BComplexity%5D))</a>] -- I think Compound Het is in a field called ‘Complexity’ in ClinVar, but I don’t see that field in the data dictionary.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FHIR-27137</th>
<th>Clarify the representation of wild type in variant profile</th>
<th>Bob Dolin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need proposal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FHIR-19829</th>
<th>Inclusion of Sanger confirmation information</th>
<th>Mullai Murugan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could be a component, extension, or a whole obs. Need to scope out</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MolSeq

<table>
<thead>
<tr>
<th>FHIR-24682</th>
<th>MolecularSequence.referenceSeq.genoBuld should align with obsGenFinding.component.ref-sequence.assembly</th>
<th>Larry Babb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Might need to consider search parameters</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FHIR-19373</th>
<th>Consider support for sending VCF data</th>
<th>Gil Alterovitz</th>
</tr>
</thead>
</table>
Chat History:

From Rachel Kutner (Epic) to Everyone: (11:18 AM)

Questions posed to labs:

Are Variant Consequence (defined by the SO concept "Structural Variant") and Functional Effect (SO concept "Functional Effect") the same as ClinVar’s terms for “Molecular Consequence” and “Functional Consequence”?

a. Molecular consequence: a calculation of the effect of the sequence change, reported per transcript. ClinVar calculates the predicted molecular consequence, but does not predict functional consequence.

b. Functional consequence (e.g. quantitative effects on gene expression, alternative splicing) is based on experimental evidence and must be submitted.

Do you use Variant Consequence or Functional Effect when providing genomic results?

a. How do you define them?

b. Where do you get the terms used for resulting them (e.g. “Loss of heterozygosity” or “5' UTR”)? Would it make sense to combine these concepts and result them together in the same place?

From Arthur Hermann to Everyone: (11:29 AM)

Do you use Clinvar and/or Sequence Ontology? Do you need to use Clinvar (or other) labels in your reporting?

We use Molecular Consequence Sequence Ontology (SO) terms to calculate our variant names and to aid in variant interpretation, but they are not directly used or displayed in the report data. When experimental data is available in the literature then we will also take the Functional Consequence of the variant into consideration for variant interpretation. This is captured through Sherloc evidence codes (PMID: 28492532). We do not use ClinVar data in our reporting, but do reference ClinVar Variation IDs where available for the general information of the clinician.

From Bret H to Everyone: (11:54 AM)

yep pardon. dna chg type loss of heterozygosity under functional effect in so

FHIR Subgroup Meeting June 15th, 2020

We are ZOOMing away from FCC. New coordinates:

[https://zoom.us/j/2980068716](https://zoom.us/j/2980068716)

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16. Liz Amos - NLM - liz.amos@nih.gov
17. Bret Heale - Intermountain Healthcare - bheale@gmail.com
18. Scott Robertson - Kaiser Permanente - scott.m.robertson@kp.org
19. Kevin Power - Cerner - kpower@cerner.com
20. May Terry - MITRE - mayT@mitre.org
21. Bob Dolin - Elimu Informatics - bdolin@elimu.io
22. Arthur Hermann Kaiser Permanente arthur.hermann@kp.org
23. Ning Xie - BWH - nxie1@bwh.harvard.edu
24.
25.
26.

http://sequenceontology.org/browser/current_svn/term/SO:0001060

Agenda:

1. Variant annotations
   a. (How) Do you use ontological terms in your workflow for variant annotation?
      i. Do you use Clinvar and/or Sequence Ontology? Do you need to use clinvar (or other) labels in your reporting?
      ii. Note that these terms are separate from inheritance and pathogenicity, etc
      iii. Jamie: Suggest pointing to clinvar definitions as our prototype model for gap analysis.
      iv. Clem: make sure we get them to look at a straw man to see what they think about it
   
   b. ClinVar’s **Molecular Consequence** is a well-defined concept:
      i. Molecular consequence represents effects on protein products from the alterations in the coding nucleotide sequence. NCBI computes molecular consequence, and also assigns location-based ontology terms established by [Sequence Ontology (SO)](https://www.sequenceontology.org), based on where the variant is located relative to gene, RNA and/or coding regions.
      ii. These are “close to” ground truths
      iii. Liz: Not *submitted* to clinvar, but are present in the database as calculated by NCBI
   c. ClinVar’s **Functional Consequence** is a larger bucket for terms that are either experimentally observed or predicted
i. Functional consequence is an observed effect of a sequence change on function. Ontologies such as VariO and Sequence Ontology (SO) are used to standardize terms. As used by NCBI's resources, functional consequence is experimentally determined, in contrast to molecular consequence, which is computed from sequence annotation.

2. Other topics for next week+
   a. Where we will eventually put them:
      i. Liz: don't see the value in pointing to individual branches in SO, could just bind to SO (in general) and provide guidance to describe the terms to select
      ii. Bret: it can add value in displaying reports downstream
      iii. Kevin: hard to get LOINC on board without pointing them to a list
      iv. Clem: answer lists without questions are like free electrons, they need to be connected

b.

Discussion:

1. Variant annotations
Rachel:
My understanding of our problem statement (and what I sent to labs when reaching out and asking for input) is as follows:

1. Are Variant Consequence (defined by the SO concept "Structural Variant") and Functional Effect (SO concept "Functional Effect") the same as ClinVar's terms for "Molecular Consequence" and "Functional Consequence"?
   a. Molecular consequence: a calculation of the effect of the sequence change, reported per transcript. ClinVar calculates the predicted molecular consequence, but does not predict functional consequence.
   b. Functional consequence (e.g. quantitative effects on gene expression, alternative splicing) is based on experimental evidence and must be submitted

2. Do you use Variant Consequence or Functional Effect when providing genomic results?
   A. How do you define them?
   b. Where do you get the terms used for resulting them (e.g. “Loss of heterozygosity” or “5' UTR”)?

3. Would it make sense to combine these concepts and result them together in the same place? First, does this align with your understanding of what we want to achieve during this discussion? What changes would you suggest (additions, alterations, clarifications) to make this clearer or more accurate?
   Second, should I update the original Jira trackers now that we have had a few discussions on this? Would it be best to consolidate the two trackers (for “Variant Consequence” https://jira.hl7.org/browse/FHIR-27748 and “Functional Effect” https://jira.hl7.org/browse/FHIR-27747 ) into one, with the above questions as the description?

From Liz Amos:
1. Get an idea how important these concepts are to lab's resulting
2. Understand how extensively the terms in the SO are applied (they're very specific and likely more granular than results require) and whether they fully overlap with what the lab uses to result (if applicable)
3. Ask for definitions from each lab - what these concepts mean in context of genomic resulting (if applicable)
4. Ask if the ClinVar definitions/concepts sufficiently represent these fields/terms as the labs result them. If not, discuss why.

I'm not an expert, but it looks like every term under SO's "structural variant" (http://sequenceontology.org/browser/current_svn/term/SO:0001537) may be able to be calculated explicitly from the type and location of the variant. We should confirm this and then we could push for using the larger list as it aligns with Clinvar's "Molecular Consequence."

However, Clinvar's guidance on the "Functional Consequence" concept is very spotty, and we need to be careful there. @Liz Amos do you have any contacts related to that effort? Kevin and I uncovered some discrepancies... Additionally, their data dictionary lists several terms that are also under "structural variant" in SO, so the move to binding this concept to the sister SO term "functional_effect_variant" (http://sequenceontology.org/browser/current_svn/term/SO:0001536) should be deliberate, if made.

We may need to separate out consequences not based on where they are in SO but on how they were asserted. I'm looking to the IM work to help out here, and think it should be included in our "lab ask."

CHAT: From Bret H to Everyone: (11:11 AM)
- perhaps it is 1 do you use clinvar or so encodings? if they're not encoding at all , even in the back end with either then it's up to us 2 here's a list of terms, put them into catagory A or catagory B.
- use a survey service like redcap, or surveymonkey

From Bret H to Everyone: (11:28 AM)
- personally, I would like to see both these NLM/NIH funded projects get together and agree. we've a ton of databases funded by the US government that overlap and choose to remain disjointed.
- where does the responsibility for consensus on publically funded projects lie
From mayterry to Everyone: (11:28 AM)
- +1 with Bret.

From Bret H to Everyone: (11:31 AM)
write your congressman about the waste in rework and expense in crossmapping...hmmm

From Bret H to Everyone: (11:54 AM)
Patrick’s use case was for display for recipient of report. his system can’t calculate. sry. must dash. good discussion. keep the question simple. and this is not necessarily for the lab it’s for the recipient
From mayterry to Everyone: (12:00 PM)
And the recipient being?…providers? That’ll potentially determine how complex we need this to be.

FHIR Subgroup Meeting June 8th, 2020

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5. Bob Dolin - Elimu Informatics - bdolin@elimu.io
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7. Hayden Bader - Epic - hbader@epic.com
8. Lingteng -BWH tenglingling@gmail.com
9. Kevin Power - Cerner - kpower@cerner.com
10. Ning Xie - BWH - nxie1@bwh.harvard.edu
11. Scott Isaac - Epic - scisaac@epic.com
12. Lloyd McKenzie - Gevity - lmckenzie@gevityinc.com
13. Liz Amos - NLM - liz.amos@nih.gov

Agenda:

2. Diagnostic Report
   a. Category vs code for indexing (https://jira.hl7.org/browse/FHIR-19831)
      i. Current code for Genomics Report is *Not valid* per LOINC
ii. Confirmed that category is searchable - but need to force our GE slice 1..1 - jamie to find other tracker here

iii. Can still use genetics “GE” category to search for genomic reports, frees code slot up for describing the scope of the report/testing done.
   1. Current binding is LOINC - (some ambiguities here, not all LOINCs are valid for reports)
      a. WG should explore the value in identifying a list of genomics report codes
         i. BobM - would like a code to signify the report is related to HLA gene family, consider usage of additional coding here vs putting it somewhere else
      b. Patrick - FHIR shouldn’t be completely bound to all rules and terms set in place by LOINC
      c. Kevin - let’s keep this tracker scoped to remove binding on code,
      d. Patrick to log new tracker for identifying what/how to bind it
      e. Dan Rutz- agree, should request labs to list codes they like to use here
      f. Bret - may consider LOINC groups on that tracker. Can we get more details from Swapna/others?
         i. https://search.loinc.org/searchLOINC/search.zul?query=Genetics%3Atrue
         ii. Explore intensional Value set to list loincs that apply here on new tracker

3. MolSeq
   a. Call for use cases/trackers
      i. Bob D: does MolSeq apply to a single molecule or not? Precision FDA quality use case is more about alignments etc
      ii. Bob M: we use it for representing the full diff of the reference - on a single molecule.
         Patrick: Couldn’t this be represented as a DiagnosticReport with contained Variants?
         Bob M: Maybe, will investigate. It can represent the whole instance of what was found. Can use a reference to help define it, and can be done definitionally
      iii. Bob D: labs outside of HLA may be doing less work to determine what a single molecule is here, we just see that there are variants
      iv. Bob M: observedSeq is 0..1 so currently can’t be properly used to describe multiple molecules
      v. Bob D: the quality metrics are about comparing your vcf to a gold standard vcf
   b. Bob M: should log another tracker to remove redundancies - in ways to define variants both through MolSeq or through a report with a list of variants.
c. Patrick: some fields may not be necessary, could be better suited to just be linked to vcf
   i. There was work a few years ago that Ira Lubin was involved in for developing a Clinical Grade VCF
      1. https://europepmc.org/article/pmc/pmc5417043
      2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5417043/
      4.

4. Variant
   a. Annotations vs Effects (variant annotation/consequence terms)
      i. Clem: vote we move to align mostly with clinvar as it is the bigger effort
         1. Currently bind to Sequence Ontology, and clivar uses SO terms, but need to identify a better (use clinvar's??) list of answer terms rather than pointing to their parent(s)
         2. Send clinvar annotation list to group and try to get some lab partners on call

b. Removal of components - discussion ongoing

Discussion:

1. DR
2. Variant

<table>
<thead>
<tr>
<th>Variant</th>
<th>FHIR-27748</th>
<th>Rename &quot;Functional Annotation&quot; Component to &quot;Variant Consequence&quot;</th>
<th>Rachel Kutner</th>
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<td>Update answer list for Mode of Inheritance LOINC code</td>
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<tr>
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<td>Liz+Clem to update code and list with terms from HPO</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Liz: will need a new code - requested</td>
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<td>Confirm (w/ clinvar etc) that compound heterozygous has a home or</td>
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appropriate way to communicate - may be more appropriate as tied to the phenotype than the variants themselves


-- I think Compound Het is in a field called ‘Complexity’ in ClinVar, but I don’t see that field in the data dictionary.

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<td>Larry Babb</td>
<td>Might need to consider search parameters</td>
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<td>FHIR-16398</td>
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3. MolSeq

FHIR Subgroup Meeting June 1st, 2020

We are ZOOMing away from FCC. New coordinates:

https://zoom.us/j/2980068716

Find your local number: https://zoom.us/u/adNIRW2P8J

Quick link to this sign-in/notes document: tinyurl.com/fhirgenomics

Sign In: (presiding co-chair - Jamie Jones)

14. Bob Milius - NMDP/CIBMTR - bmilius@nmdp.org
15. May Terry - MITRE - mayT@mitre.org
16. Rachel Kutner - epic - rkutner@epic.com
17. Liz Amos - NLM - liz.amos@nih.gov
Agenda:

1. Open JIRA overview
2. Stress Testing IG Implications with Examples

Discussion:

5. Open JIRA overview
   a. variant annotation/consequence terms - narrow down the question of what we are resolving
      i. Labs need to be able to accurately represent data they return as results.
      ii. Need to reconcile terms either through clinvar, ensembl, and (the base of both of these to some extent) Sequence Ontology.
      iii. Missing: Stakeholder group of 5-10 laboratories currently using
      iv. Dan: can continue to get some of this through O&O, many labs work more closely with that group. Definitely able to get pointed answers on that side, if we can target questions.
   
   
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| Variant        | FHIR-27748   | Rename "Functional Annotation" Component to "Variant Consequence" | Rachel Kutner | desire to reconcile this area of SO closely with clinvar and ensembl. Rachel: variant consequence [https://m.ensembl.org/info/genome/variation/prediction/predicted_data.html](https://m.ensembl.org/info/genome/variation/prediction/predicted_data.html)
|                |              |                                                              |               | Clinvar: molecular consequence: a calculation of the effect of the sequence change, reported per transcript. ClinVar calculates the predicted molecular consequence, but does not predict functional |
consequence. Functional consequence (e.g. quantitative effects on gene expression, alternative splicing) is based on experimental evidence and must be submitted.

Bob M: same as variant effect prediction?
https://useast.ensembl.org/info/docs/tools/vep/index.html

### Variant

| FHIR-27747 | New Component for Functional Effect | Rachel Kutner | Suggest persuasive, Liz: consider functional consequence in clinvar
Bob D: sounds like a great homework problem before locking down a set of terms here. Between SO, ensembl, clinvar.
Clem: clinvar is very widely used and should be heavily favored unless strong evidence otherwise.
|
| variant (also loinc) | FHIR-27743 | Update answer list for Mode of Inheritance LOINC code | Rachel Kutner | loinc list was created for eye-gen. Gtr has an authoritative list that uses HPO terms.
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<td>Ideal strategy for handling a large amount of genomic results. Method needed to describe what things you looked at and didn't touch.</td>
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6. **Stress Testing IG Implications with Examples**

7. **new guidance**

**region studied**

**new guidance**

**new guidance**

**molSeq**

**implications**

**implications**

**implications**

**implications**

**implications**

**implications**

**family member history**

**duplicate**

**CORE**
Chat not reflected elsewhere:

here is the snpEff list, which apparently is now drawn from Sequence Ontology (see section ‘Effect prediction details’: http://snpeff.sourceforge.net/SnpEff_manual.html#input

From Bret H to Everyone: (11:54 AM)

with removal or moving of components with loinc codes found in the hl7 v2 guide, we will need to tell people where it's gone

---

**FHIR Subgroup Meeting MAY 18th, 2020**

We are ZOOMing away from FCC. New coordinates:

[https://zoom.us/j/2980068716](https://zoom.us/j/2980068716)

Find your local number: [https://zoom.us/u/adNIRW2P8J](https://zoom.us/u/adNIRW2P8J)

**Quick link to this sign-in/notes document:**

[tinyurl.com/fhirgenomics](https://tinyurl.com/fhirgenomics)

Sign In: (presiding co-chair - Jamie Jones )

1. Kevin Power - Cerner - kpower@cerner.com
2. May Terry - MITRE - mayT@mitre.org
3. Liz Amos - NLM - liz.amos@nih.gov
4. Bret Heale - Intermountain - bheale@gmail.com
5. Bob Dolin - Elimu Informatics - bdolin@elimu.io
6. Daniel Rutz - Epic - drutz@epic.com
7. Hayden Bader - Epic - hbader@epic.com
8. Lloyd McKenzie - Gevity - lmckenzie@gevityinc.com
9. Patrick Werner - MOLIT - pw@molit.eu
10. Joel Schneider - NMDP/CIBMTR - jschneid@nmdp.org
11. Scott Isaac - Epic - scisaac@epic.com
12. Clem McDonald - NLM - clemmcdonald@mail.nih.gov
Agenda:

1. Connectathon review
2. Next steps
3. JIRA (didn’t cover)

Discussion:

1. Connectathon review
   a. CAT 24 Report out
   b. CG connectathon 24 links
      i. Representing variants in apps (https://molit.eu/variant-viewer/) Still very beta, configurable rewrite is done at the moment.
         1. Webcomponents contained here:
            https://github.com/molit-institute/fhir-components
         2. Docs here:
            https://docs.molit.eu/fhir-components/#/components/MolecularReport
         3. Currently - Need to support ALL possible configurations/representations to display. Choosing only one method may not be sufficient
   4. Producing reusable open source web components
      a. Patrick is a gift
   5. Clem’s group working on GUI questionnaire with some bioinformatic logic built in
      a. SPDI as a partial check on validity, hoping to integrate with mutalyzer
   ii. $find-subject-variants
      1. Syntactic normalization - use API to display variants using the same components regardless of how it was provided to server
      2. Semantic normalization - aligning different representations of the ‘same variant’ e.g CCC > CC vs CC > C.
         a. SPDI effective tool for indels that look like this
      3.
   iii. STU2 implication reporting
         a. Questions over integration with problem list
         b. Condition.evidence?
      3. This example can trigger some interesting discussion around our usage of ‘Associated Phenotype’ Ties back to this JIRA:
And the Zulip discussion here:

iv. FSH - FHIR shorthand for creating structureDefinitions
   1. Current Beta version of sushi pulls all IG configurations into one yaml file, does more than just create structure definitions, can initialize a whole IG with template - open questions on long term support and scope in that regard (question of whether it should just restrict itself to structureDefinitions)
      a. https://github.com/FHIR/sushi/releases/tag/v0.13.0-beta.1
   2. Technical concerns around lack of round tripping from structure definitions. Proof of concept work in progress

v. QA - outdated artifacts pull request for R5
   1. Review current core build for straggling references to old profiles
   2. Guidance on MolecularSequence remains for now (no other guidance on it exists)
   3. Merits full review

2. Next steps:
   a. Looking ahead
      i. https://www.devdays.com/us/schedule/
      ii. Sept Connectathon
      iii. Content freeze?
   b. Priorities before STU2 freeze
      i. Variant components
         1. 3 JIRAs
      ii. Finalize implication update
         1. associated phenotype/cancer stress test
         2. 10 JIRAs
      iii. TBD-LOINC
         1. 1 JIRA, may need more
   iv. TMB, MSI
      1. Example validation
   v. Region Studied
      1. 3 JIRAs, examples needed
   vi. MolecularSequence??
      1. 2 JIRAs, may need more

3. JIRA (37 open issues)

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<td>Ideal strategy for handling a large amount of genomic results. Method needed to describe what things you looked at and didn't touch.</td>
<td>Apurva Dharia</td>
<td></td>
</tr>
<tr>
<td>new guidance</td>
<td>FHIR-16406</td>
<td>Add plans for future mappings to R4</td>
<td>Gil Alterovitz</td>
<td></td>
</tr>
<tr>
<td>new guidance</td>
<td>FHIR-16404</td>
<td>Add group doc STU3 to STU4</td>
<td>Gil Alterovitz</td>
<td></td>
</tr>
<tr>
<td>new guidance</td>
<td>FHIR-16402</td>
<td>Add material from guidance document</td>
<td>Gil Alterovitz</td>
<td></td>
</tr>
<tr>
<td>molSeq</td>
<td>FHIR-24682</td>
<td>MolecularSequence.referenceSeq.genomeBuild should align with obsGenFinding.component.ref-sequence.assembly</td>
<td>Larry Babb</td>
<td></td>
</tr>
<tr>
<td>molSeq</td>
<td>FHIR-19373</td>
<td>Consider support for sending VCF data in Sequence</td>
<td>Gil Alterovitz</td>
<td></td>
</tr>
<tr>
<td>molSeq</td>
<td>FHIR-16398</td>
<td>Add detail to quality matrix</td>
<td>Gil Alterovitz</td>
<td></td>
</tr>
<tr>
<td>implications</td>
<td>FHIR-26945</td>
<td>clarifying 'context' vs 'risk-of' for associated phenotype and/or associated cancer component</td>
<td>Bret Heale</td>
<td></td>
</tr>
</tbody>
</table>
FHIR Subgroup Meeting MAY 11th, 2020

We are ZOOMing away from FCC. New coordinates:
https://zoom.us/j/2980068716
Find your local number: https://zoom.us/u/adNIRW2P8J
Quick link to this sign-in/notes document:
tinyurl.com/fhirgenomics

Sign In: (presiding co-chair - Jamie Jones )

1. Kevin Power - Cerner - kpower@cerner.com
2. Bob Dolin - Elimu Informatics - bdolin@elimiu.io
3. Liz Amos - NLM - liz.amos@nih.gov
4. Dora Finkeisen - MOLIT Institut - dora.finkeisen@molit.eu
5. Bret Heale - intermountain - bheale@gmail.com
6. Alex Mankovich - Philips - alex.mankovich@philips.com
7. Hayden Bader - Epic - hbader@epic.com
8. Peter Muir MD - Peter@PjmConsultingLLC.com
9. Rachel Kutner - Epic - rkutner@epic.com
10. Ning Xie - BWH - nxie1@bwh.harvard.edu

implications | FHIR-26426 | Add new component for ‘Potential Clinical Trial Match’ | Kevin Power
implications | FHIR-26380 | describe adverse effects on Implication | James Jones
implications | FHIR-26379 | Support for detailed lab text on Implications | James Jones
implications | FHIR-25170 | relatedArtifact extension on Observation.component | James Jones
implications | FHIR-20198 | Medication Impact profile obs-med-impact (CG IG) | Larry Babb
implications | FHIR-19844 | PGx High Risk Allele Medication Impact is confusing | Larry Babb
implications | FHIR-19244 | Level of Evidence CodeableConcept should have some kind of binding | Patrick Werner
implications | FHIR-16175 | Genetic Impact - Add ACMG reference for level of evidence | Kevin Power
implications | FHIR-16082 | PGx Impact - Allele functional status | Kevin Power
family member history | FHIR-15886 | Missing the Ancestry profile in the IG | Xin Liu
duplicate | FHIR-16493 | Relation of PgX Example to Specimen analyzed to produce Diagnostic Report results | Andrea Pitkus
Agenda:

1. Example report statements
2. Other topics

Discussion:

1. Example report statements regarding phenotypes and/or cancers
   a. associated phenotype/cancer stress test
      i. Please list name and or link to report
   b. Example Reports
2. What about additional use cases not coming directly from reports?
   a. Bob D. ACMG screening and PGx screening against external information
   b. Confirm with tinyurl.com/damcgdoc
3. Connectathon 24 updates - stay tuned!
4. Joint with O&O prep - define extensions and get feedback send around details
   a. Concern of where the text should be attached - Observation.note, components, report sections
   b. May be interesting to add an Observation component to capture patient age at time of testing - no tracker yet, Bret to check on other options
   d. mCODE extensions - http://hl7.org/fhir/us/mcode/artifacts.html#3
      i. Scope is larger - models cancer as a Condition and uses extension to reference, a few other needs

**FHIR Subgroup Meeting MAY THE 4TH, 2020**

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9. Peter Muir - Peter @PjmConsultingLLC.com
10. Michelle Barry-Availity, LLC -michelle.barry@availity.com
11. Joel Schneider - NMDP/CIBMTR - jschneid@nmdp.org
12. Ning Xie - BWH - nxie1@bwh.harvard.edu
13. Bob Milius - NMDP/CIBMTR - bmilius@nmdp.org

Agenda:

1. Connectathon updates
2. Discriminating discriminators
3. TBD concepts
4. Level of Evidence vs Clinical Significance (did not address)

Discussion:

1. Connectathon updates
   a. Update based on last week’s tuesday notes
   b. Creating and validating genomic reports
   c. GACS server will be available
   d. Encourage folks to register (only $100) and fill out survey

2. Discriminating discriminators
   a. Spreadsheet parsing is unsupported. But build seems to work -structuredefinition
   b. Still need to confirm “profiling a profile” errors

3. General QA
   a. Try adding code system with content=not present
   b. Special-url parameter list in the top json file in IG file structure- differentiate “internal” urls
i. For validating a local code system (e.g., genenames.org/ <- which doesn’t exist as we define it)
ii. https://chat.fhir.org/#narrow/stream/215610-shorthand/topic/Codesystems.20and.20Valuesets
   1. special-url - "If a canonical resource in the IG should actually have a URL that isn’t the one implied by the canonical URL for the IG itself, it must be listed here explicitly (as well as defined in the resource itself). It must be listed here to stop it accidentally being different. Each canonical url must be listed in full as present on the resource; it is not possible to specify a pattern."
   c. Consider example.org urls
d. Canonical examples - easy homework problem!
e. Patrick pushing MSI+TMB
   i. Need to add to diagrams and consider other guidance areas

4. TBD concepts

<p>| Current status: |
|-----------------|-------------------------------------------------|---------------------------------|-------------------------------|
| grouper         | grouper                                         | A means to bundle several       | No answers needed              |
|                 |                                                 | observations such as one would   | Our own concept. Needs         |
|                 |                                                 | find in a genetics test panel.   | formal writeup                 |
| mode-of-inh    | mode-of-inhance                                 | This is actually LOINC code      | Jamie will remove              |
| inheritance    |                                                 | 79742-3. And the IG will be     |                               |
|                 |                                                 | updated                         |                               |
| effect-tran     | effect-tranporter-funct| Predicted phenotype for drug     | Referenced list, needs        |
| transporter-funct| tion                                            | efficacy through transport      | curating                      |
|                 |                                                 | mechanism. A single marker      | Referenced concept. Needs      |
|                 |                                                 | interpretation value known to    | curating                      |
|                 |                                                 | increase or decrease the drug’s |                               |
|                 |                                                 | performance.                    |                               |
| effect-med      | Medication                                      | Referenced list, needs          | Jamie will update and          |
| medication-effi | Efficacy                                         | curating                        | remove                        |
| eacy            |                                                 |                                 |                               |
| effect-med      | Medication                                      | Referenced list, needs          | Jamie will update and          |
| medication-     | Metabolism                                       | curating                        | remove                        |
| metabolism     |                                                 |                                 |                               |</p>
<table>
<thead>
<tr>
<th>term</th>
<th>definition</th>
<th>status</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>effect</strong></td>
<td>medication transporter function</td>
<td>Referenced list, needs curating</td>
<td>Duplicate, remove</td>
</tr>
<tr>
<td><strong>effect</strong></td>
<td>high risk allele</td>
<td>NEEDS THOUGHT, open trackers</td>
<td>Referenced concept. Needs curating</td>
</tr>
<tr>
<td><strong>prognostic</strong></td>
<td>implication component</td>
<td>Finding of whether a particular somatic genotype/haplotype/variation or combination-thereof predicts a particular outcome for the specified cancer - either on its own or in conjunction with one or more interventions.</td>
<td>unbound</td>
</tr>
<tr>
<td><strong>associated</strong></td>
<td>cancer</td>
<td>Associated Cancer</td>
<td>unbound</td>
</tr>
<tr>
<td><strong>associated</strong></td>
<td>therapy</td>
<td>Genomically linked therapy</td>
<td>unbound</td>
</tr>
<tr>
<td><strong>region-coverage</strong></td>
<td>Given as a number between 0 and 100. Mean mapped read depth. Obtained by counting total number of mapped reads and divided by the number of bases in the region sequence.</td>
<td></td>
<td>Needs writeup</td>
</tr>
<tr>
<td><strong>functional-annotation</strong></td>
<td>Annotated changes to sequence features caused by this variant. Terms are from the sequence ontology under SO:0001537.</td>
<td></td>
<td>Concern over answer list? Needs writeup</td>
</tr>
<tr>
<td>exact-start and end</td>
<td>Variant exact start and end</td>
<td>The genomic coordinates of the exact genomic range in which the variant resides.</td>
<td>Update original LOINC?</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>inner-start and end</td>
<td>Variant inner start and end</td>
<td>The genomic coordinates of the inner genomic range in which the variant might reside.</td>
<td>Update original LOINC?</td>
</tr>
<tr>
<td>outer-start and end</td>
<td>Variant outer start and end</td>
<td>The genomic coordinates of the outer genomic range in which the variant might reside.</td>
<td>Update original LOINC?</td>
</tr>
<tr>
<td>variant-inheritance</td>
<td>Variant inheritance</td>
<td>A quality inhering in a variant by virtue of its origin. The terms are in the sequence ontology under SO:0001762</td>
<td>Needs writeup</td>
</tr>
<tr>
<td>diagnostic-implication</td>
<td>Diagnostic Implication</td>
<td>An observation linking a genomic finding with a knowledge base, providing context that may aid in diagnosing a patient with a particular phenotype or condition.</td>
<td>No answers needed</td>
</tr>
<tr>
<td>therapeutic-implication</td>
<td>Therapeutic Implication</td>
<td>An observation linking a genomic finding with a knowledge base, providing potential evidence of an interaction with a specified medication or non-medicinal therapy.</td>
<td>No answers needed</td>
</tr>
</tbody>
</table>

Next steps:
1. Jamie will remove extra one
2. Several just need writeup for our own profiles (grouper, diagnostic/therapeutic implications)
3. 3 positional loincs need reconciliation with original codes
4. 2 SO-based concepts need writeup and sent to loinc
5. 2 PGx concepts with lists need thought (after updating)
6. Associated-cancer (need to explain concept fully and mention 1-2 preferred bindings)
   a. What system to push? Currently unbound -
      i. preferred to ICD-O-3
ii.  snomed/etc
iii.  HPO or possibly Disease Ontology?

7.  Associated phenotype
8.  Diagnostic phenotypes vs potentially associated
   a.  Current modeling is that found in lab’s report - pointing out potentially associated
       concepts.
   b.  Ongoing discussion with O&O re: obs vs condition
   c.  Need example reports for actual diagnoses
   d.  Current examples:  
       https://drive.google.com/drive/u/0/folders/18T4RS0VnrJdLS3k79skbrZ0cYyL1U53t
   e.  Need to reconsider strength of diagnoses and implications. Towards implementing a
       decision support layer on top of our IG.
       i.  Additional (parallel) components for stronger statements?
       ii.  Decision support IG profiling the universal IG?
       iii.  Suggest conditions on diagnostic profiles mirroring our usage of tasks in pgx?
   f.  JIRA discussing this (comments welcome) :  https://jira.hl7.org/browse/FHIR-26945

5.  Level of Evidence vs Clinical Significance
   a.  https://loinc.org/93044-6/ (currently preferred list)
   b.  https://loinc.org/53037-8/ (currently extensible list)
   c.  Issue: AMP conflates concepts, should it be separated out?

Previous notes:
https://docs.google.com/document/d/1p8xD-iNiujhUJhrNI9gAUrj1yeY-Tp_hnlqawPoweAl/edit#heading=h.yntd678x4fjv