HL7 Clinical Genomics Specs Convergence Roadmap

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CG Specifications Overview

**v3:**
- Family History (Pedigree) Topic

**v2:**
- v2 Implementation Guides
  * The Clinical Genomics implementation guides are based on the HL7 Version 2.5.1 Laboratory Result Reporting
  * New topics / releases are still being developed

**CDA:**
- A CDA Implementation Guide for Genetic Testing Reports (GTR)

** Deprecated:**
- Genetic Locus / Loci
- Genetic Variations Topic
- Gene Expression Topic

**Under Development:**

**FHIR:**
- Sequence resource
- A number of profiles

**Common:**
- Domain Analysis Model (DAM)
- Domain Information Models (DIM) describing the common semantics
- The IM effort strives to standards-independent DIMs aligning all specs
Why Multiple HL7 Spec Families?

• Presumably – each family has its ‘orientation’:
  • v2/v3 – message specs
  • CDA- document spec
  • FHIR – API

• But – they all carry similar data!

• So, what could be done?
  • Could CG specs be converged to a single standard?
    • Doesn’t seem probable as HL7 supports all spec families
    • However, converge CDA and FHIR seems possible if done over FHIR Composition (possibly with some extensions)
  • Keep the various specs but align them by the DIMs
    • Useful only if they are tightly mapped to DIMs
Why Documents?

CDA

Human-to-Human

Printed
Bedside
...

Machine-to-Machine

EMR
Transcription
...

Structured data

Clinical Decision Support
Patient held-records alerts
...

Structured data

Medical Records
Transformation
...

Interlinks

Narrative ↔ Structured Data Co-existence…
Document Main Characteristics

- **Context** - A clinical document establishes the default context for its contents.

- **Persistence** – A clinical document continues to exist in an unaltered state, for a time period defined by local and regulatory requirements.

- **Stewardship** – A clinical document is maintained by an organization entrusted with its access control given proper confidentiality & consent.

- **Potential for authentication** - A clinical document is an assemblage of information that is intended to be legally attested by well-defined authorship including signatures as required.

- **Wholeness** - Authentication of a clinical document applies to the whole and does not apply to portions of the document without the full context of the document.

- **Human readability** – A clinical document is human readable.
CDA Structure

- CDA – a *generic* specification

- Could be used to represent various types of documents:
  - Consultation note
  - Visit / progress note
  - Referral letter
  - Discharge summary
  - Operative note
  - …

- A document type is also called ‘template’ or ‘implementation guide’
Documents and Interoperability

Based on IHE XDS*

Source: NHIN specifications, 2010

*IHE XDS = Integrating the Healthcare Enterprise – Cross Enterprise Document Sharing
Documents and Interoperability

epSOS – European Patients Smart Open Services

Source: epSOS project documentation (funded by the EU and carried out by the countries HIT national agencies, e.g., NICTIZ, GEMATIC, etc.)
Documents and Interoperability

• Most major regional / state interoperability efforts used documents (e.g., HIE organizations in the US)

• Clinical documents were the payload whether it was with XDS registry or through a p2p exchange (e.g., NHIN Direct)

• CDA was the most common base payload schema
CDA and FHIR

Documents vs APIs

- Documents are the correct way to exchange information between clinicians in disparate parts of the healthcare system.
- APIs will integrate access to the data between applications where the context is unambiguous.
- Both the document and API should seamlessly use the same syntax and semantics and Narrative approach.

Source: Graham Grieve presentation on CDA and FHIR
The HL7 CG GTR* Structure

• The document consisted of sections:
  • Summary (1..1)
  • Test details (1..*)
  • Background information (0..*)

• The Summary section:
  • Consisted of an overall interpretation
    • Summarizing several genomics test interpretations in a study (e.g., hearing loss)
  • Also - recommendations

• The Test Details Section:
  • Consisted of test’s info described in detail
  • Each section related to a certain test

* GTR was published in 2013
• A panel is actually a study, similarly to the notion of study in medical imaging (e.g., CT & MRI to study a lesion)
• The study document can hold the context in the best way
• A document can also be easily exchanged
• Attestation (& signatures) and other ‘medical records’ prosperities are explicitly represented

Source: Iowa Head and Neck Protocols
1. GJB2 – Sequencing

2. GJB6 - 2 Deletions

3. Mitochondrial DNA - 2 Mutations

http://ltd.aruplab.com/Tests/Pub/2001992
* example results (as used in the HL7 v2 and GTR spec documentation)
• The OtoGenome™ Test targets individuals who have a diagnosed hearing loss whose underlying etiology has not yet been identified
• Goals & context expand to hearing loss and related syndromes
• OtoGenome™ Test includes 87 Genes
• Source:
GTR Example*

* For illustration only; the complete instance can be found here: hearing loss
Summary

Indications

- Indication: Profound sensorineural hearing loss

Specimen and Genomic Source Class

- Peripheral Blood
- Genomic source class: Germline

Summary of Tests Performed

- GJB2 Full Gene Test
- GJB6-D13S1830 deletion
- Mitochondrial Hearing Loss Mutation Test

Overall Interpretation

- Inconclusive.
- DNA sequencing detected two changes in the GJB2 gene, 79G>A (V27I) and 109G>A (V37I). The V27I change has been reported as a benign variant (references) and is not believed to cause hearing loss. The V37I mutation has been previously reported in patients with hearing loss. This mutation, in homozygosity or combined with another GJB2 disease causing mutation, typically results in a mild to moderate hearing loss (Cryns et al. 2005). Mutations in both copies of the GJB2 gene are necessary to assume that GJB2 is responsible for the hearing loss. Although two mutations were identified in this patient, we would assume that the combination of a benign variant and a mild pathogenic mutation would result in a mild to moderate hearing loss rather than a moderately-severe one, as in this patient. It is most likely that the hearing loss in this patient is the result of the V37I mutation and an unknown second pathogenic mutation. It should be noted that a second mutation is not identified in a large percentage (10-50%) of patients with nonsyndromic hearing loss and GJB2 mutations (del Castillo et al. 2003).
- GJB6-D13S1830 Deletion: A PCR-based analysis of the GJB6-D13S1830 region of chromosome 13 was performed and did not detect the deletion. This test does not assess the DNA sequence of the GJB6 gene or detect other mutations that could affect the expression of the gene.
- Mitochondrial Hearing Loss mutations: Targeted bidirectional sequencing of mitochondrial DNA 1555 and 7445 regions did not detect the presence of these mutations.

Recommendations

- Although some cases may represent a coincidental carrier state, all of the studies have concluded that there are likely to be other genetic mutations that have not yet been identified. Genetic counseling is recommended for this patient and his/her family members.
GTR Example

Genetic Variations

Tests Performed

- GJB2 Full Gene Test

Findings

- DNA MUTATIONS: Heterozygous 109G>A (V37I), Exon 2, GJB2, Pathogenic
- INCIDENTAL VARIANTS: Heterozygous 79G>A (V27I), Exon 2, GJB2, Benign

Interpretation

- DNA sequencing detected two mutations in the GJB2 gene, 79G>A (V27I) and 109G>A (V37I). The V27I mutation has been reported as a benign variant (references) and is not believed to cause hearing loss. The V37I mutation has been previously reported in patients with hearing loss. This mutation, in homozygosity or combined with another GJB2 disease causing mutation, typically results in a mild to moderate hearing loss (Cryns et al. 2003). Mutations in both copies of the GJB2 gene are necessary to assume that GJB2 is responsible for the hearing loss. Although two mutations were identified in this patient, we would assume that the combination of another GJB2 disease causing mutation, and a mild pathogenic mutation would result in a mild to moderate hearing loss rather than a moderately-severe one, as in this patient. It is most likely that the hearing loss in this patient is the result of the V27I mutation and an unknown second pathogenic mutation. It should be noted that a second mutation is not identified in a large percentage (10-50%) of patients with nonsyndromic hearing loss and GJB2 mutations (del Castillo et al. 2003).

Genetic Variations

Tests Performed

- GJB6-D13S1830 Deletion Test

Findings

- Negative.

Interpretation

- GJB6-D13S1830 Deletion: A PCR-based analysis of the GJB6-D13S1830 region of chromosome 13 was performed and did not detect the deletion. This test does not assess the DNA sequence of the GJB6 gene or detect other mutations that could affect the expression of the gene.

Genetic Variations

Tests Performed

- Mitochondrial Hearing Loss Genes Test

Findings

- Negative.

Interpretation

- DNA sequencing did not detect the presence of any mutations in the MTTS1 and MTRNR1 genes.
Could CDA & FHIR be Converged?

• Port the HL7 GTR CDA-based to FHIR using Composition

• Profile the Composition resource and name it:
  • “Genomics Study Document”

• Leverage FHIR Genomics:
  • Leverage the profile DiagnosticReport-Genetics to represent the structured data in a certain Test Details section
  • Rename the profile to “Genomics Test Report”
  • The other parts should follow my ballot comments on FHIR Genomics of Sep. 2016
• GenomicsStudyReport document includes multiple genetic tests and summary with overall interpretation

• GenomicsTestReport represents a single genetic testing and holds its interpretation

• Variants reside solely in Genomics Observation, optionally pointing to observed and reference sequences

• Sequence can be both observed or reference, using the same construct

• ‘Phenotype’ represents any type of analysis results towards clinical utilization, e.g., ‘relevance’, ‘significance’, ‘interpretation’, etc.

Same ‘phenotype’ construct is shared by the three levels of analysis to achieve semantics consistency across the spec
Roadmap to Converge CDA & FHIR

Same Phenotype construct is shared by the three levels of analysis

Single Sequence structure
HL7 Sequence Design Principles

• Sequence should hold merely sequence data (observed, reference,...)

• Sequence should not contain any information that is the result of downstream analysis (i.e., beyond assembly of the sequence itself)

• Sequence should include metadata about the sequence, e.g., quality, provenance, pointer to repository holding the full sequence, etc.

• Sequence could encapsulate (inline) a sequence portion if it’s key to its association to ‘phenotypic’ data and not larger than limits posed by the wire spec (e.g., FHIR)
  • In which case, native formats should be used (i.e., any bioinformatics format commonly used in the industry to represent sequences)
  • HL7 Sequence should not provide yet another format to represent sequences as it’s out of scope for ‘Clinical Genomics’ (as the work group name implies)
Future Work – Elaborate on Phenotype

• The gist of clinical genomics is the ‘gen-phen’* association
• Most efforts thus far focused on the genomics side
• Genomics is covered by bioinformatics communities

• The term ‘phenotype’ in this proposal:
  • Represents any type of analysis results towards clinical utilization, e.g., ‘relevance’, ‘significance’, ‘interpretation’, etc.
  • Can be replaced with a consensus term, if we find such...

• Phenotypes are complex
  • Especially if all semantics is included explicitly as needed by CDS
  • E.g. hearing loss with certain genetic variants, at certain age range and being on certain antibiotics
  • Need to develop a more robust and expressive model for phenotypes
  • E.g., ‘Phenotype statement’ involving conditions, medications, etc.
  • Extend the ‘related observation’ value set to represent a more precise ‘gen-phen’ semantics

* The phrase ‘gen-phen’ is used here to represent the association itself, therefore - ‘gen’ is not limited to genotypes rather ‘gen’ represents any omics data.