Supporting interoperability of genetic data with LOINC

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ABSTRACT

Electronic reporting of genetic testing results is increasing, but they are often represented in diverse formats and naming conventions. Logical Observation Identifiers Names and Codes (LOINC) is a vocabulary standard that provides universal identifiers for laboratory tests and clinical observations. In genetics, LOINC provides codes to improve interoperability in the midst of reporting style transition, including codes for cytogenetic or mutation analysis tests, specific chromosomal alteration or mutation testing, and fully structured discrete genetic test reporting. LOINC terms follow the recommendations and nomenclature of other standards such as the Human Genome Organization Gene Nomenclature Committee's terminology for gene names. In addition to the narrative text they report now, we recommend that laboratories always report as discrete variables chromosome analysis results, genetic variation(s) found, and genetic variation(s) tested for. By adopting and implementing data standards like LOINC, information systems can help care providers and researchers unlock the potential of genetic information for delivering more personalized care.

Key words: Genetics, LOINC, Medical records systems, Clinical laboratory information systems, Vocabulary, controlled

INTRODUCTION

Strong arguments exist for delivering molecular genetic test results to electronic health records (EHRs) as standards-based, structured (computable) electronic reports for clinical and research purposes.[1–4] The fact that most genetic tests apply for a lifetime and may have to be automatically reinterpreted as new knowledge becomes available[3] only strengthens these arguments. Logical Observation Identifiers Names and Codes (LOINC; Regenstrief Institute Inc, Indianapolis, IN) and HL7 (Health Level Seven International, Ann Arbor, MI) are the mainstays for structured reporting of routine laboratory test results.[5] These 2 key standards also provide a framework for structured reporting of genomic tests[6] in conjunction with widely accepted vocabulary standards for naming genes and genetic variations.[3,7–9] In this report, we will describe LOINC's approach to naming/coding genetic tests (and their results), its scope, its mechanisms for gathering new content, and its current limitations.

LOINC

LOINC is a universal code system developed by the Regenstrief Institute for identifying laboratory tests and clinical observations in electronic messaging.[10] The current release[14] contains more than 73 000 terms, covering the full scope of laboratory testing (chemistry, microbiology, etc) and a broad range of clinical measurements (eg, vital signs, electrocardiograms, patient reported outcomes, clinical document titles,[11,12] and radiology reports[13,14]). LOINC includes a data model for representing answer lists, panels of individual observations, other details like help text, and units of measure.[15] New versions of the standard are published twice yearly. LOINC has been widely adopted as the standard for laboratory test result names in the United States, where it is a national standard,[16,17] and internationally.[18,19] Many genetic test reporting initiatives,[20,21] including the HL7 Clinical Genomics Working Group,[22,23] have adopted LOINC.

Here we focus on the 1400+ LOINC terms currently used in human genetic test reporting. Documentation and downloads of the entire LOINC database are available at http://loinc.org.

Naming conventions in LOINC

Each LOINC term has a fully specified name containing 6 main axes (Component/Analyte, Property, Timing, System/Specimen, and Method). The axes produce names detailed enough to distinguish among similar observations.[18] For naming genetic tests that target specific genetic variations, LOINC uses the Human Genome Organization Gene Nomenclature Committee's terminology[24] to name the gene(s) and the Human Genome Variation Society's (HGVS) syntax to name the variation(s)[25] of interest. We are aware of the challenges due to misnaming and version changes in these nomenclatures[26]; however, the thousands of LOINC users tend to detect and report such problems. Updates to LOINC terms follow best practices.[27] Where updates do not alter the meaning, we correct "wrong" portions of the name and keep the old names as synonyms. Alternatively, a

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new term can be created and the old term retired, adding a forward link to the new term.

Scope of LOINC coverage

LOINC provides codes for a broad range of human molecular genetic and cytogenetic tests. Here we provide a sampling of the LOINC content so that laboratories will be better able to understand and use LOINC terms for ordering and reporting. Many laboratories report the "simpler" genetic tests as individual and computer-understandable HL7 Version 2 observations in a way similar to the reporting of routine chemistry and hematology tests. These simpler kinds of genetic tests are the ones most commonly ordered in primary care,[28] and LOINC has observation codes available for most of them.

Tests for specific gene mutations

As of July 2014, LOINC carries 192 terms for reporting single mutations (variants) qualitatively as present or absent, eg, *HFE gene.p.C282Y [21695-2]*—the variation most commonly associated with hereditary hemochromatosis in Caucasians. It also carries a quantitative measure of single mutations, eg, *JAK2 p.V617F mutant/control [53761-3]*—a report on the prevalence of white cells with the variation associated with polycythemia vera. Both of these examples use HGVS nomenclature as part of the test name. The National Center for Biotechnology Information's (NCBI) Single Nucleotide Polymorphism database (dbSNP) codes[29] may also be embedded in LOINC test names, especially when the variation is outside of the coding region, eg, *IL28B gene associated variant rs12979860 [60279-7]*. LOINC also contains nearly 50 codes for trinucleotide repeats, including both qualitative tests with answers like *not expanded*, *intermediate*, or *expanded*, and quantitative tests that report the actual number of repeats, eg, *HTT gene.CAG repeats [53782-9]*.

Tests for chromosomal alterations

Many chromosomal alteration tests can also be reported as computer-understandable observations using one or more LOINC codes. For example, LOINC contains codes for qualitative studies for trisomies and uniparental disomies, eg, *Chromosome 21 trisomy [Presence] [21771-1]*. Today, aneuploidy risk can also be estimated by quantifying the dosage of chromosome-specific circulating cell-free DNA in maternal plasma *[see 73970-6]*, and such tests are revolutionizing prenatal testing.

A variety of LOINC codes are available for reporting structural chromosome rearrangements. For example, BCR-ABL1 testing for diagnosis and management of blood cell malignancies is reported qualitatively as *t(9;22)(q34.1;q11)(ABL1,BCR) b2a2+b3a2 fusion transcript [42714-6]*. The following 2 approaches exist for reporting the ratio of a BCR-ABL1 fusion transcript to a control transcript: the raw transcript to control ratio *[e.g., 55147-3]*, and a transformed ratio based on an international standard *[e.g., 69380-4]*. To increase computability, tests that report a chromosomal alteration, such as BCR-ABL1, should also report the results using the International System for Human Cytogenetic Nomenclature (ISCN)[30,31] when possible.

Fully structured reporting of molecular genetic and cytogenetic tests

LOINC collaborated with HL7 to provide codes for all of the variables contained in two HL7 Clinical Genomics Working Group implementation guides for structured reporting of genetic tests—one for reporting genetic variations[23] detected via sequencing, gene chips, and other methods, and another for reporting the results of cytogenetic studies.[22] All of the LOINC codes in these 2 implementation guides include guidance on how they are to be used, and the categorical variables are linked to specific sets of allowed answers.

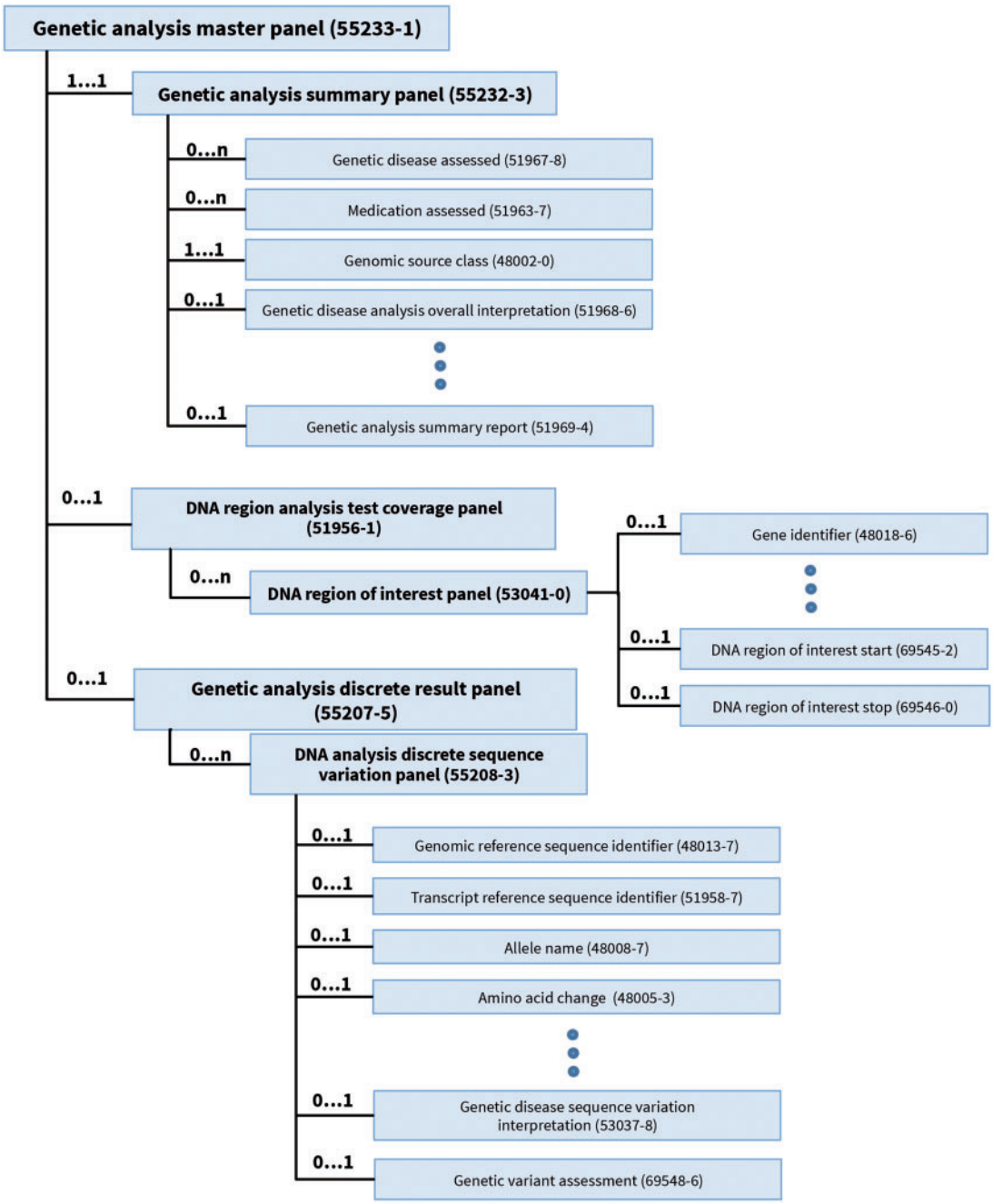
The genetic variation collection consists of a number of LOINC panels, including one that reports the overall results of the study, another that reports the details about each variation found, and yet another that describes the region of interest and the gene chip as applicable (see figure 1). To improve the integration of cytogenetic test results into EHRs, Heras et al[18] examined a range of sample cytogenetic test names and result reports and, from this empirical effort, created a LOINC-enabled HL7 specification for reporting cytogenetic tests in a fully structured form.[22] The LOINC codes for this specification are organized under the *Chromosome analysis master panel [62389-2],* which includes a choice of subpanels for discrete reporting of the 3 major testing approaches—chromosome banding, fluorescence in situ hybridization, and microarrays. Variables in this collection include the genomic source class (eg, germline, somatic), genetic disease assessed, chromosome analysis in ISCN nomenclature, and overall interpretation (for microarray example, see figure 2).

Mutation analysis tests

These HL7 definitions have not yet been adopted widely, however; and molecular genetic tests, especially those for large numbers of variations, tend still to be reported as free-text narrative.[28] To accommodate this reality and provide a standard way to order and report such tests, LOINC provides terms that include the gene name(s) and phrase *mutation analysis*. Currently LOINC distinguishes among the following different types of mutation analyses:

1. Mutation analysis for a specific gene or genes that target a fixed set of important mutations. Example: *APC gene mutation analysis [20990-8]*.
2. Mutation analysis limited to one or more known mutations previously found in a family member. The mutations tested vary by patient. Example: *ACADVL gene mutation analysis limited to known familial mutations [73736-1]*.
3. Full mutation analysis targeting the entire coding region in the targeted part of the genome. Example: *ACADVL full gene mutation analysis . . . by sequencing [73735-3]*.
4. Mutation analyses for deletions/duplications. Example: *ACVRL1 gene + ENG gene deletion and duplication mutation analysis [69481-9]*.

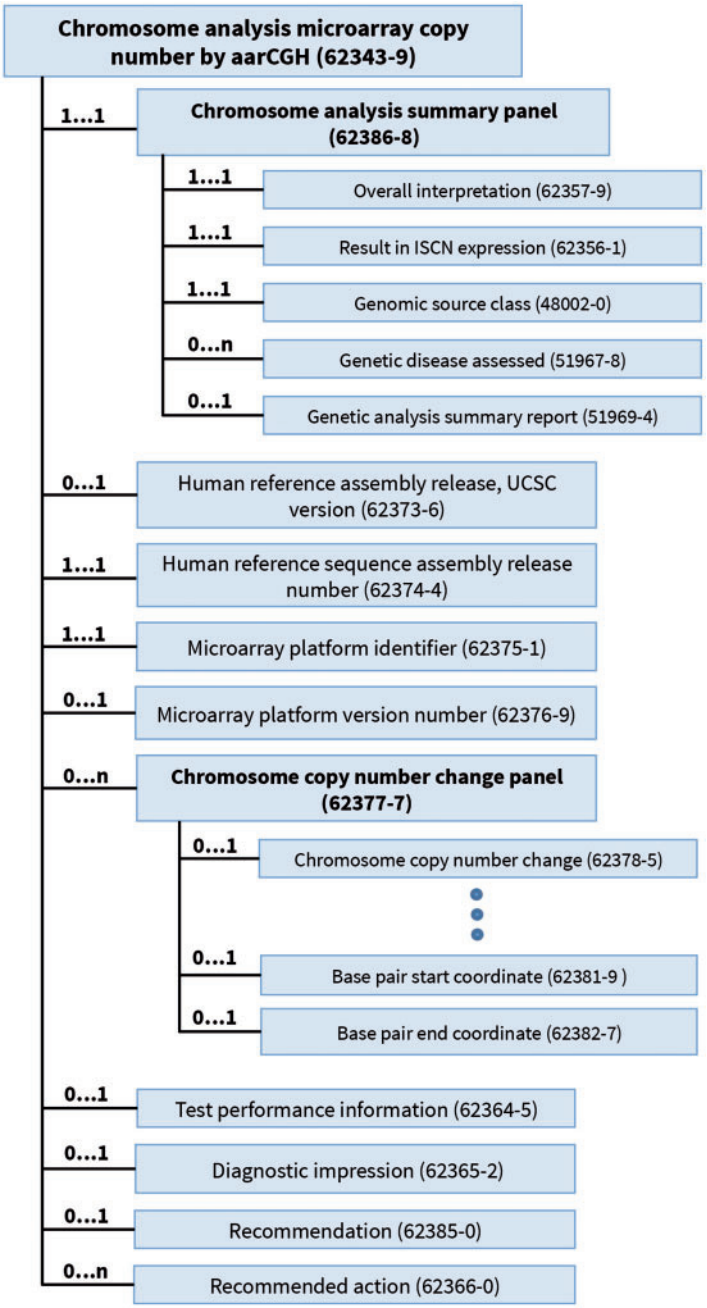
Figure 1: Genetic analysis master panel.



Augmenting narrative reports

Because we anticipate the transition to a fully structured molecular genomic reporting will take time, we encourage services that report their content as narrative reports to also include LOINC terms to deliver the core results in a computer-understandable form. Specifically, for mutation analysis studies, we encourage the inclusion of one LOINC term that reports the mutations found (eg, *APC gene mutations found [20990-8]*) and another that reports the mutations that could have been found. For tests that report only a fixed set of mutations, this can be done with 1 additional observation—*APC gene mutations tested for [21618-4]*. For sequencing and other tests to deliver the same information about what could have been found, terms from the *DNA region of interest panel [53041-0]* can be included as additional observations. All genetic studies should also include an observation that reports the reference sequence with a LOINC term such as *Reference sequence Identifier [48012-9]*.

Figure 2: Chromosome analysis microarray copy number change panel, included within the Chromosome analysis master panel (*62389-2*) (not shown here).



Cytogenetic tests that are delivered as narrative should include an additional observation that provides the findings in ISCN nomenclature to provide computability,[30,31] eg, *Chromosome analysis result in ISCN expression [62356-1]*. However, it is better to provide the report in Heras's full structured cytogenetic specification.[18,22] Cytogenetic tests should also include an observation for the reference assembly build identifier such as *Human reference sequence assembly release number [62374-4]*.

Result values for LOINC genetic codes

The use of LOINC codes to identify genetic tests is 1 ingredient for interoperability. Standards on the result values used to report the variations detected are equally important. Full details about the recommended result values for each code, ranging from Systematized Nomenclature of Medicine–Clinical Terms (International Health Standards Development Organization, Copenhagen, Denmark) to HGVS syntax, are provided in the LOINC database and in the HL7 implementation guides. In

general, LOINC recommends the use of HGVS syntax for reporting variations and encourages the use of a second identifier, such as NCBI's dbSNP[29] or ClinVar[32] IDs or, in the case of somatic mutations on cancer specimens, COSMIC[33] (Genome Research Limited, Hinxton, UK) IDs. Since an HL7 Version 2 OBX-5 result field can carry 2 independent coding systems, both the HGVS notation and an alternative identifier can be reported together. For reporting pharmacogenomics genetic test results, LOINC encourages the use of the star-allele nomenclature[34–36] as an additional way to report results because it is so widely used. For cytogenetic studies, ISCN is the standard nomenclature used to report genomic rearrangements identified either by standard karyotyping or molecular methodologies.[30]

Mechanisms for contributing to LOINC content

Almost all of LOINC's content is based on external requests from laboratories, instrument vendors, test kit vendors, and public health departments around the world. Regenstrief welcomes requests for new LOINC terms. Submitters are asked to provide information for each variable requested, including a proposed LOINC name, a definition for the new analyte or method, units of measure for quantitative variables, answer lists for categorical variables, package inserts when a test is marketed, and deidentified sample reports when needed to understand the structure of test panels (see LOINC Users' Guide[37] for full details). Even with this amount of information, the LOINC team invests time in further research to enrich the definitions, verifying that existing LOINC terms do not satisfy the request and ensuring consistency across the database. The naming conventions in LOINC are informed by the input we receive from requestors and volunteer experts and are guided by the Laboratory LOINC Committee that meets twice a year in open meetings.

LIMITATIONS AND CHALLENGES

LOINC has substantial coverage of existing laboratory tests, but it is never complete. We hope to reach the point where we create LOINC codes for all tests in their premarketing stage. We are at that point for the test kits that the Centers for Disease Control distributes externally and may reach the same point for at least one large in vitro diagnostics vendor. LOINC lacks tests for whole exome and whole genome testing, including some of the newest whole genome microarray and high-resolution comparative genomic hybridization tests,[38] because we have not yet received requests for them.

Variation in the styles for reporting genetic test results poses a substantial challenge to standardization. For example, some laboratories report variants identified on each allele as separate variables (eg, Allele 1 = TPMT*2, Allele 2 = TPMT*3C). Others report the value of both alleles as a single variable with a 2-part answer (eg, TPMT*2/*3C). In both cases, the allele naming style also varies considerably. One laboratory may include both the gene name and the allele name in the answer, another may report only the allele name, and yet another may report wild type and the letter code for the nucleotide result for the non–wild type. Further, some laboratories may only report presence or absence of a specific variant. We had discussions with the Food and Drug Administration about determining 1 standard approach to report the value of 2 alleles and providing guidance to the laboratory kit and instrument industry accordingly. They were open to this idea but have not yet acted.

CONCLUSION

The need to integrate genetic data with EHRs is compelling. LOINC is a widely adopted standard that provides codes to improve interoperability of genetic test reporting, including fully structured discrete reporting, tests for specific chromosomal alterations or gene mutations, and narrative cytogenetic or mutation analysis reports. By adopting and implementing data standards like LOINC, information systems can help clinicians unlock the potential of genetic information for delivering more personalized care.

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CONTRIBUTORS

JD and DJV conceived, wrote, and edited the manuscript. They are both guarantors. CJM provided critical revisions to the manuscript. All of the authors read and approved this manuscript for publication.

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COMPETING INTERESTS

None.

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