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HL7 Version 2 Implementation Guide: Clinical Genomics Coded Reporting – Lite, Release 1 (1st Informative Ballot), U.S. Realm

Informative Ballot

September 2016

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**Sponsored by: Orders and Observations Work Group and Clinical Genomics Work Group**

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|  |  |  |
| --- | --- | --- |
| Name | Organization | Role |
| Hans Buitendijk | Cerner Corporation | Orders & Observations Work Group Co-Chair |
| Ulrike (Riki) Merrick | Vernetzt, LLC | Orders & Observations Work Group Co-Chair |
| Mollie Ullman-Cullere | Better Outcomes Corp. | Clinical Genomics Work Group Co-Chair and Principal Contributor |
| Gil Alterovitz | Boston Children's Hospital | Clinical Genomics Work Group Co-Chair |
| Siew Lam | Intermountain Healthcare | Clinical Genomics Work Group Co-Chair |
| Bob Milius | National Marrow Donor Program | Clinical Genomics Work Group Co-Chair |
| Amon Shabo | Philips Healthcare | Clinical Genomics Work Group Co-Chair |
| Clement J. McDonald | National Library of Medicine | Principal Contributor |
| Donna Maglott | National Library of Medicine | Contributor |
| Swapna Abhyankar | Regenstrief Institute | Contributor |
| Rebecca Goodwin | National Library of Medicine | Contributor and Editor |
| Ajay Kanduru | National Library of Medicine | Contributor |
| Shennon Lu | National Library of Medicine | Contributor and Editor |
| Paul Lynch | National Library of Medicine | Contributor |
| Daniel J. Vreeman | Regenstrief Institute | Contributor |
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Notes for Reviewers

Ballot reviewers, questions are listed throughout this guide in **bold red font** to make them easy to review in context. Please closely review and respond to the issues and questions in the following places:

* Section 1.3.3 (RE: Change from use of OBR-OBX nesting to OBX-4 dot notation).
* Section 1.3.4 (RE: CWE.1 and CWE.2).
* Section 3.1 (RE: Publicly available tables for some coding systems of interest).
* Table 1, Row 7 (RE: ISCN codes).
* Table 1, Row 9 (RE: Ensembl and UniProtKB protein reference sequences).
* Table 1, Row 11 (RE: HGNC and NCBI codes).
* Table 2, Row A.7 (RE: LOINC #51959-5 ranges of DNA sequence examined).
* Table 2, Row A.11 (RE: LOINC #51969-4 Full narrative report).
* Table 3, Row B.15 (RE: LOINC #48001-2 Chromosome location of genetic variant)
* Table 3, Row B.16 (RE: LOINC #48002-0 Genomic source class)
* Table 4, Row C.3 (RE: LOINC #81298-2 Structural variant cytogenetic location).
* Table 4, Row C.4 and Row C.5 (RE: LOINC #81290-9 Structural variant HGVS expression and LOINC #81291-7 Structural variant ISCN).
* Table 5, Row D1.3 (RE: Cross reference to genetic details).
* Table 5, Row E1.2 (RE: LOINC #82116-5 Medication usage suggestion [type]).
* Section 5.5 (RE: a variable for HGVS expressions at the genomic level).
* Section 5.7 (RE: Change from the use of OBR–OBX nesting to OBX-4 dot notation and its implementation.

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# Introduction

The *HL7 Version 2 Implementation Guide: Clinical Genomics Coded Reporting – Lite, Release 1 (1st Informative Ballot) – US Realm, Standard for Trial Use, July 2016* is based on collaborative efforts between the HL7 Clinical Genomics Work Group, the HL7 Orders and Observations Work Group, and the Health and Human Services Standards and Interoperability Framework Laboratory Result Interface Working Group.

## Purpose

Currently the majority of genetic tests are reported as purely narrative reports with no computer accessible coding. This could enable the delivery of some information that could be used in decision support and medical record queries and be easily adopted by clinical laboratories that now report results in HL7 v2.x. There is a need for an easier mechanism in V2 messaging to communicate genomic reports that are a mix of narrative and structured data. The goal is to encourage and make it easier for genomic reporting services to add some coded result information to the purely narrative (or PDF) reports they often send in HL7 V2 messages. It is not intended to satisfy all of the needs of all genomic studies, for which there is ongoing work to develop a comprehensive genomic reporting standard.

Some genomic studies do currently report some content as structured codes. These typically have the mutation name in their test name and report whether that mutation is present or absent. An example is LOINC code 24475-6 “F2 gene c.20210G>A [Presence]...”. However, more complicated genetic analyses are usually reported as pure narrative with no computer understandable coding. Such reports may have LOINC names for the overall report with names like “full mutation analysis with sequencing as the method” or “targeted mutation analyses” that report only whether a selected set of mutations is present or not. A special case of targeted mutation analyses -- those that target only known familial mutations -- test a patient for the few specific mutations known to be present in a relative.

## Audience

Laboratories, hospitals, providers, public health, government agencies, pharmaceutical.

### Relevant Laboratory Implementation Guides

This implementation guide is based on the 2013 [HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model (US Realm)](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=23).

This guide also incorporates much of the content of the [HL7 Version 2.5.1 Implementation Guide: S&I Framework Lab Results Interface (LRI), Release 1 DSTU Release 2](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=279), which was the result of collaborative efforts between HL7 and the Office of the National Coordinator (ONC) Standards and Interoperability (S&I) Framework Laboratory Results Interface (LRI) Initiative.

### Requisite Knowledge

* [HL7 Version 2.5.1 Implementation Guide: S&I Framework Lab Results Interface (LRI), Release 1 DSTU Release 2](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=279)
* [HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model (US Realm)](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=23), 2013
  + Referenced throughout this document as the 2013 HL7 Clinical Genomics Implementation Guide (or V2IG\_CG\_LOINCGENVAR\_R2\_INFORM\_2013MAR)
* [HL7 Version 2 Implementation Guide: Clinical Genomics; fully LOINC-Qualified Cytogenetic Model, Release 1 - US Realm](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=364), 2014
* HL7 OIDs: <http://www.hl7.org/oid>
* LRI: [Standards and Interoperability Laboratory Results Interface (LRI) Use Case, Laboratory Results Reporting to Primary Care Providers (in an Ambulatory Setting) v1.0](http://sibrowser.siframework.org/siclient/view?type=artifact&id=39481918-9dc7-4f55-aa77-f978b4c13d8b&name=SIFramework_LRI_UC.docx)
* LOINC: <http://loinc.org/>
  + [LOINC Manual (aka User’s Guide)](https://loinc.org/downloads/files/LOINCManual.pdf)
  + [LOINC Quick-Start Guide](http://loinc.org/get-started)

## Key Technical Decisions

This guide is intended as a profile on top of HL7 Version 2.5.1 Implementation Guide: S&I Framework Lab Results Interface (LRI), Release 1 DSTU Release 2. Where silent, this guide adopts the provisions in LRI. We are anticipating several changes in the next release of LRI (US Realm), as described below, to adopt features that are now used in HL7 V2, or proposed extensions of such features.

### An important new HL7 feature – Repeat Values – for OBX-5

Be aware that in this implementation, users can list many independent codes as a list separated by the repeat delimiter tilde symbol (~) within the value field (OBX-5) of one OBX. For long lists of values for genes included in a study and mutations targeted, this will provide a more compact report with fewer OBXs. So we encourage its use. This feature is required to express the answers to variables in Table 2 Rows A.3 and A.6, as well as in Table 5 Rows D1 and D2, where mutations in two different genes combine to affect drug metabolism or efficacy.

### Support for Numeric Range (NR) Data Type

The Numeric Range (NR) HL7 data type is used to specify the lowest and highest values in a series of data. This guide uses the NR data type for a number of variables in the specification (e.g. LOINC #51959-5 Ranges of DNA sequence examined -- See Table 2 Row A.7) to specify the start and end location of the DNA sequence. The NR data type is supported by HL7 V2 and FHIR, but not yet supported by the LRI lab specification. We have asked that NR be allowed in the next release of LRI, and to allow repeated NR values in one OBX-5 as described above for coded data types. At present in HL7 V2 each repeat of an NR requires a separate OBX, and the OBX-4 values will have to differ among such repeats. We recommend 1.1, 1.2, 1.3 etc.

### The change from the use of OBR–OBX nesting to OBX-4 dot notation and its implementation

The 2013 HL7 Clinical Genomics Implementation Guide for clinical genetics reporting (*HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model, Release 2 (HL7 V2IG CG LOINCGENVAR R2-2013*) included a number of nested LOINC panels. It used nested OBR- OBX relationships to represent that nesting in the message. The HL7 Clinical Genomics Work Group thought that it would probably be easier to represent that nesting in OBX-4 using dot notation (like a Dewey decimal), which also conforms with LRI. So that is how we have implemented it. The message is still defined conceptually by a hierarchy of LOINC panels (as shown in the example/definition). But this hierarchy is expressed by the dot notation in OBX-4 rather than as parent-child relationships between OBRs and OBXs. The message contains just one OBR, which will carry the code for the order code.

See examples in Table 2 through Table 6, and additional detailed description in Section 5.7.

**Balloters please opine on whether we should stay with this approach or re-consider the OBR–OBX structure.**

### Miscellaneous issues regarding coding systems and the convention for this guide

We think of coding systems as having a code, a name (print string) and a code system -- the historic HL7 triplet. However, what goes in which of these three slots can be ambiguous in some cases.

First we have codes (such as the HGNC gene codes) and associated attributes. These codes identify a record that carries the code and two “names”, the symbol (e.g. “[CFTR”) that is used most commonly in discourse, and the full name “cystic fibrosis transmembrane conductance regulator](http://www.genenames.org/cgi-bin/gene_symbol_report?hgnc_id=HGNC:1884)” that is not used as often. The coding system we defined for genes uses the Symbol as the “name”, and we crafted the name so that it would not collide with a coding system created in the future that used the full name as the “print string” for the coding system.

The second case: While HGNC genes file has too many names, some coding systems lack an obvious name. The dbSNP database, which carries more than 150 million “rs” codes, does not have an assigned name. This situation occurs with many kinds of codes, e.g. the zip code. These kinds of codes have no ambiguity about what should be in the code slot. It should be the code. We have two choices about what to put in the name slot, and decided to repeat the code there rather than leaving it blank, in case some systems expect something for display in the “name” slot; and that is what you will see in the example OBX-5 in Table 2 through Table 6 and in all of the examples in Section 6.

The third case occurs with the “code systems” that do not have anything that looks like a traditional code made up of letters and numbers. This is the case for syntaxes like UCUM, HGVS, and ISCN. We have made the same choice: we put the syntax in both the first and the second slot, for the same reasons we did it with code-only code systems.

**Balloters: The alternative would be to record either kind of code in CWE.1 and leave CWE.2 blank. What is the preferred approach?**

There are some evolving cases. The gene location is one. The content is defined by a syntax, and most sources only record the name. But there have been attempts in the past to enumerate and apply codes to them. Some of those efforts have disappeared, but we are still hoping we can find an authoritative source for a listing that also includes an obvious code. At the present we are treating it as a syntax (as it is), but if we find a coded enumeration in the timeframe of the balloting process we will incorporate it.

### Harmonizing with FHIR

We believe this V2 message could be represented as a FHIR diagnostic report with linkage to raw or other special chunks of Sequence data within the Sequence profile. The FHIR analogue of this proposed V2 structure would carry the OBX content described in this guide as FHIR observations. A panel of observations could be described as a set of components of the panel “observation” (the cleanest way if it works out), or via components *and* related observations. At present FHIR does not permit multiple values in a single observation field, so we would have to treat those multiples as separate observations. But between the component and the associated observation we are fairly sure we could implement all of the relationships specified in this V2 version. We are working with Lloyd McKenzie to mock up a pilot analogue of this structure as a FHIR Diagnostic report in parallel with the balloting of this document. When the V2 message is close to acceptance we would want to work with the FHIR sequence developers to see if the two approaches could be harmonized.

# Scope

## In Scope

* Reporting one or more simple genetic variants – those with changes in 50 or fewer contiguous nucleotides that do not act together to define a phenotype.
* Reporting structural and copy number variants – those with changes in 51 or more contiguous nucleotides, often including very large variants, tens of thousands or millions of nucleotides in length. Reporting pharmacogenomics studies, which look for simple or complex variants that affect the rate of metabolism or the efficacy of one or more drugs, and often include suggestions about possible change in dosing or the use of a different drug. These may or may not be linked to the very specific details reported about other types of variants covered in this guide.
* Reporting complex variants – those made up of one or more simple variants which together define or influence a phenotype. Haplotypes and Compound Hets are examples of complex variants. This guide provides variables for reporting information about the complex variant as a unit and for reporting full details about related simple variants using the same variables as used for reporting unrelated simple variants.
* Reporting germline and somatic mutations.

## Out of Scope

* Non-human genetic studies -- In future revisions, it may be easy to extend this guide to other vertebrates and/or eukaryotes, but they are not part of this guide.

LOINC already supports the many specialized ways that public health and clinical care uses NAAT studies for detecting microorganisms and susceptibility genes in those creatures -- and that content will persist as it is – or evolve as needed to accommodate that special requirements of such testing.

* Single mutations that have long been reported as single tests with the HGVS mutation in the name, e.g. LOINC # 244475-6 F2 gene c.20210G>A [Presence].
* Gene/chromosome fusions and other such studies (and trinucleotide repeats) that are often reported quantitatively as the number of blood cell containing the anomaly or the ratio of a marker gene to the abnormal gene in cells or as a single ISCN code. Trinucleotide repeats are also reported as quantitative values (e.g. number of repeats) with existing LOINC codes.
* Commercial Cell Free Prenatal studies and DNA based colon cancer screening tests which at present report conclusions and risk for various anomalies but not any raw genetic data. (Though we hope that they will move toward the reporting style illustrated in this guide in the future.)

# Code Systems

Successful message implementation requires that transmitted messages (message instances) contain valid values for coded fields. It is important to note that code sets can be subject to change between publications of these Implementation Guides.

## Code systems used to report values in OBX-3, OBX-5 and OBX-6 in this guide.

Table 1 carries all of the coding systems used in this guide, one per row. These are all defined in the HL7 OID Registry (<http://www.hl7.org/oid/index.cfm>). Each row includes information from the HL7 OID table including their HL7 link names, long names, and OIDs. For each coding system, this table also includes a definition/description, and when available either a URL that provides an overview of the source table for that coding system, a URL that permits viewing/exploring the content of that table and/or a URL for downloading that table. There are more than 25 coding systems in the table. One of these, LOINC, is used to identify the observations in the message (OBX-3). Another one, UCUM, is used for coding units of measures (OBX-6); however, in this guide, few quantitative measures have units of measure. The remaining code systems provide codes for variables that use coding systems to report their values (OBX-5). This table only includes *external* coding systems, such as ICD-9-CM and SNOMED CT and NCBI/EBI genetic content. It does not include the short answer lists that are linked to specific LOINC terms in the LOINC database. You will find these short answer lists associated with LOINC codes in the next set of tables (Table 2 through Table 6), which identify the LOINC observations used in this guide, and each row includes the LOINC term for each observation along with LOINC definitional content, such as the description, cardinality and either the answer list codes or the coding systems from which answers shall be drawn. The links between observations and their answer lists/coding systems are also implemented in a web-based tool called LHC-Forms, developed by the Lister Hill National Center for Biomedical Communications (LHC), U.S. National Library of Medicine (NLM). The LHC-Forms clinical genomics demonstration form (See Figure 2) carries all of the observations that may be included in a Clinical Genomics Lite message, (<https://lforms-demo.nlm.nih.gov/>). When you enter text into a field for a categorical observation in this form you will see the options (from the LOINC short answer lists or the coding system) pop up as an autocomplete.

Some of the coding systems in this table can be enumerated and can be found in tables at their sources’ web site. These enumerated tables are in some cases quite large (e.g. dbSNP’s table carries 150 million rows). Others (e.g. UCUM, HGVS and ISCN) are defined by a syntax, and can’t be fully enumerated -- though tables with common subsets of such codes may be available. Syntax validity checkers are available for UCUM (http://lhncbc.github.io/ucum-lhc/) and for HGVS (https://mutalyzer.nl/).

Most of the tables that represent sources for these coding systems are available for exploration and look up at the LHC Clinical Table Search Service (<https://lforms-service.nlm.nih.gov/>) and can be explored, configured and/or used as a service by implementers. For some of these tables this service also provides direct download access to the original source table and is configured in an open downloadable form.

The URL for the page that shows what you can do with these look up tables is <http://lhncbc.github.io/autocomplete-lhc/> (and a developer’s page is available at: <https://lhncbc.github.io/autocomplete-lhc/docs.html>). The URLs for lookups and for direct downloads of specific tables appear in each row of the coding systems. The programs that deliver these autocomplete look ups are available as open source mostly JavaScript widgets or services from GitHub.

We have not completed the work of creating tables in the LHC Clinical Table Search Service for every potential coding system in this guide. For example, we have not found a publicly available electronic source table for the allele (genotype) (LOINC # 47998-0). **Balloters if you know of any such tables please let us know.**

Table 1: CODING SYSTEMS

| **#** | **Coding System name** | | **HL7 V2 Linkage Name** | **HL7 OID** | **Description and sources** |
| --- | --- | --- | --- | --- | --- |
| 1 | Cytogenetic (chromosome) location | | **Chrom-Loc** | 2.16.840.1.113883.6.335 | **Source Organization:** National Center for Biotechnology Information (NCBI)  **Source table information:** Pending  **Source table download:** Pending  **Place to Explore Table :**  https://lforms-service.nlm.nih.gov/apidoc/cytogenetic\_locs/v1/doc.html    **Description:** Chromosome location (AKA chromosome locus or cytogenetic location), is the standardized syntax for recording the position of genes and large mutations. It consists of three parts: the Chromosome number (e.g. 1-22, X, Y), an indicator of which arm – either “p” for the short or “q” for the long, and then a series of numbers separated by dots that indicate the band, sub band and sub-sub band of the locus (e.g. 2p16.3). There are other conventions for reporting ranges and locations at the ends of the chromosomes.  The table of these chromosome locations was loaded with all of the locations found in NCBI’s ClinVar variation tables. It will expand as additional sources become available. This does not include all finely grained chromosome locations that exist. Users can add to it as needed.  We have not found a table of chromosome locations with standard codes. **Balloters: if you know of a publicly available and maintained list of chromosome locations with standard codes please forward to us.**  **Balloters: Adjacent chromosome locations are sometimes cited together (e.g. as “4q23.1q23.2”) or we have also seen them as “4q23.1-q23.2” which we think is clearer. Is one strongly preferred over the other?** |
| 2 | ClinVar Variant ID | | **CLINVAR-V** | 2.16.840.1.113883.6.319 | **Source organization**: National Center for Biotechnology Information (NCBI)  **Source table information**: http://www.ncbi.nlm.nih.gov/clinvar/  **Source table download**: <ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/>  **Place to Explore Table**:  https://lforms-service.nlm.nih.gov/apidoc/variants/v1/doc.html  **Description:** ClinVar processes submissions reporting variants found in patient samples, assertions made regarding their clinical significance, information about the submitter, and other supporting data. The alleles described in submissions are mapped to reference sequences, and reported according to the HGVS standard.  ClinVar had been focused on simple variants whose length is less than 50 base pairs and complex variants composed of multiple small variants. However, it now also includes large structural variants whose break points are known precisely. So now simple, complex and structural variants with precisely defined break points can all be found in ClinVar.  The ClinVar records have a field for Allele ID and for Variant ID. All simple variants have an Allele ID. At present, all complex and most simple variants also have a Variant ID, and by the end of 2016, all simple variants will also have a variant ID.  This coding system uses the variant ID as the code and the variant name from NCBI’s "variant\_summary.txt" file as the code’s print string. The "variant\_summary.txt" file caries more than 20 useful fields, including the separate components of the variant name, the cytogenetic location, the genomic reference, etc. So based on the Variant ID, you can use ClinVar to find most you would ever want to know about the variant.  In the LHC Clinical Table Search Service and LHC-Forms, we have indexed many of these attributes to assist users and applications that need to find the ID for a particular variant. |
| 3 | COSMIC – Simple variants | | **COSMIC-Smpl** | 2.16.840.1.113883.6.320 | **Source organization**: Wellcome Trust Sanger Institute  **Source table information** : http://cancer.sanger.ac.uk/cosmic/about  **Source table download** : http://grch37-cancer.sanger.ac.uk/cosmic/download  **Place to Explore Table** : https://lforms-service.nlm.nih.gov/apidoc/cosmic/v1/doc.html  **Copyright:** Wellcome Trust Sanger Institute, http://cancer.sanger.ac.uk/cosmic/license    **Description:** This table includes only simple somatic (cancer) mutations, one per unique mutation ID. The code is the COSMIC mutation ID, and the name is constructed from Ensembl transcript reference sequences and p.HGVS that use the single letter codes for amino acids. It carries fields analogous to most of the key fields in ClinVar, but its reference sequences are Ensembl transcript reference sequences with prefixes of ENST; it specifies amino acid changes with the older HGVS single letter codes and it carries examples of primary cancers and primary tissues -- fields that are not in ClinVar.  COSMIC's source table includes multiple records per mutation -- one per submission. The COSMIC-Simple Variants table that we have extracted from the original file includes only one record per unique mutation – a total of more than 3 million records.  These contents are copyright COSMIC (http://cancer.sanger.ac.uk/cosmic/license). LHC has produced a look up table for these records, and for users to look up particular mutation IDs, both with permission from COSMIC. However, interested parties must contact COSMIC directly for permission to download these records (http://cancer.sanger.ac.uk/cosmic/license). |
| 4 | COSMIC-Structural variants | | **COSMIC-Strc** | 2.16.840.1.113883.6.321 | **Source organization**: Wellcome Trust Sanger Institute  **Source table information**: http://cancer.sanger.ac.uk/cosmic/about  **Source table download**: http://grch37-cancer.sanger.ac.uk/cosmic/download  **Place to Explore Table**: <https://lforms-service.nlm.nih.gov/apidoc/cosmic_struct/v1/doc.html>  **Copyright**: Wellcome Trust Sanger Institute, http://cancer.sanger.ac.uk/cosmic/license    **Description:** COSMIC also has files containing structural variants. These are divided into two tables, one called structural variants and one called copy number variants. In contrast, NCBI does not separate structural variants this way.    The table for this coding system derives from COSMIC's structural variation tables. The identifiers for these are pure numbers with no prefix, and each record includes information about the mutation type, the histological classification of the sample, and the primary tissue/cancer from which the sample originated. Like COSMIC simple variants, these also use Ensembl reference sequences, but uses the genomic reference sequences instead of the transcript ones (those whose codes begin with ENSG). These contents are copyright COSMIC (http://cancer.sanger.ac.uk/cosmic/license). LHC has produced a look up table for these records, also sub-setted to include only unique mutations, for users to look up particular mutation IDs with permission from COSMIC. However, interested parties must contact COSMIC directly for permission to download these records. |
| 5 | dbSNP | | **dbSNP** | 2.16.840.1.113883.6.284 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information:** http://www.ncbi.nlm.nih.gov/books/NBK21088/  **Source table download:** <ftp://ftp.ncbi.nih.gov/snp/>  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/snps/v1/doc.html  **Description:** The Short Genetic Variations database (dbSNP) is a public-domain archive maintained by NCBI for a broad collection of short genetic polymorphisms.  The SNP ID is unique for each position and length of DNA change. For example, a change of 3 nucleotides will have a different SNP ID than a change of 4 nucleotides at the same locus, but the code will be the same for all changes at the same locus and with the same length. |
| 6 | dbVar-Germline | | **dbVar-GL** | 2.16.840.1.113883.6.322 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information:** http://www.ncbi.nlm.nih.gov/dbvar/content/overview/  **Source :** ftp://ftp.ncbi.nlm.nih.gov/pub/dbVar/data/  **Place to Explore Table :** pending    **Description:** dbVar is NCBI's database of genomic structural variations (including copy number variants) that are larger than 50 contiguous base pairs. It is the complement of dbSNP, which identifies variants occurring in 50 or fewer contiguous base pairs.  DbVar contains insertions, deletions, duplications, inversions, multi-nucleotide substitutions, mobile element insertions, translocations, and complex chromosomal rearrangements.    DbVar carries structured Germline and Somatic variants in separate files. Accordingly, we have divided the coding system for dbVar the same way. This coding system represents the Germline dbVar variants. Its record ID may begin with one of four prefixes: nsv, nssv, esv and essv.  **These** are accession prefixes for variant regions (nsv) and variant calls (or instances, nssv), respectively. Typically, one or more variant instances (nssv – variant calls based directly on experimental evidence) are merged into one variant region (nsv – a pair of start-stop coordinates reflecting the submitters’ assertion of the region of the genome that is affected by the variant instances). The ”n” preceding sv or indicates that the variants were submitted to NCBI (dbVar). The prefix ”e” for esv and essv represent variant entities (corresponding to NCBI’s nsv and nssv) that were submitted to EBI (DGVa). The relation between variant call, and variant region, instances is many to one.  The LHC lookup table for dbVar germline mutations includes both variant instances (essv or nssv) and the variant region records (nsv, esv). Users can sub-select by searching on the appropriate prefix. |
| 7 | dbVar-Somatic | | **dbVar-Som** | 2.16.840.1.113883.6.323 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information**: <http://www.ncbi.nlm.nih.gov/dbvar/content/overview/>  **Source table download**: ftp://ftp.ncbi.nlm.nih.gov/pub/dbVar/data/  **Place to Explore Table** : pending    **Description**: dbVar is NCBI's database of genomic structural variations (including copy number variants) that are larger than 50 contiguous base pairs. It is the complement of dbSNP, which only contains variants occurring in 50 or fewer contiguous base pairs. It contains insertions, deletions, duplications, inversions, multi-nucleotide substitutions, mobile element insertions, translocations, and complex chromosomal rearrangements.    Germline and Somatic variants are presented in separate files. Accordingly, we have divided the coding system within dbVar the same way. This coding system represents the Somatic (mostly cancer) variants in dbVar. As is true for the Germline portion of dbVar, the record IDs for the somatic dbVar’s have prefixes of nsv, nssv, esv or essv with the leading “e” and “n” having the corresponding meaning as described above for germline or structural variant. We also include both the variant calls and variant region records in the LHC dbVar somatic variant file. |
| 8 | Ensemblgenomic reference sequence | | **Ensembl-G** | 2.16.840.1.113883.6.324 | **Source organization:** European Bioinformatics Institute (EBI) |
| **Source table information:** http://useast.ensembl.org/info/genome/genebuild/genome\_annotation.html |
| **Source table download**: <http://useast.ensembl.org/info/data/ftp/index.html>  **Place to Explore Table**: Not implemented |
| **Description:** Set of Ensembl gene reference sequences whose identifiers have a prefix of "ENSG." It only includes genomic sequences associated with genes and uses the whole build plus the chromosome number to identify chromosome reference sequences, rather than a separate set of reference sequence identifier as NCBI does. LHC has not yet produced a convenient look up table for these files, but they are available from the URL cited above. |
| 9 | Ensemblproteinreference sequence | | **Ensembl-P** | 2.16.840.1.113883.6.325 | **Source organization:** European Bioinformatics Institute (EBI)  **Source table information:** <http://useast.ensembl.org/info/genome/genebuild/genome_annotation.html>  **Source table download**: http://useast.ensembl.org/info/data/ftp/index.html  **Place to Explore Table**: Not implemented  **Description:** Set of Ensembl protein reference sequences. Their identifiers are distinguished by the prefix of "ENSP," and correspond to NCBI's "NP\_" reference sequence identifiers. LHC has not yet produced a convenient look up table for these files, but they are available from the URL cited above. |
| 10 | Ensembltranscript reference sequence | | **Ensembl-T** | 2.16.840.1.113883.6.326 | **Source organization:** European Bioinformatics Institute (EBI)  **HL7 Long Name**: Ensembltranscript reference sequences  **Source table information**: http://useast.ensembl.org/info/genome/genebuild/genome\_annotation.html  **Source table download**:  http://useast.ensembl.org/info/data/ftp/index.html  **Place to Explore Table**: Not implemented    **Description:** Set of reference sequences for transcripts of coding regions. Their identifiers all have a prefix of "ENST." There are parallels for most (if not all) of what is in Ensembl within NCBI and most of the content is shared. "ENST" parallels NCBI's "NM\_" identifiers. In general, Ensembl takes its reference sequences directly from the genomic build. NCBI may adjust its reference sequences by replacing known "mutations" with sequences that better reflect the population "normal". LHC has not yet produced a convenient look up table for these files, but they are available from the URL cited above. |
| 11 | HGNC-Symbol | | **HGNC-Symb** | 2.16.840.1.113883.6.336 | **Source organization**: HUGO Gene Nomenclature Committee (HGNC)  **Source table information**: http://www.genenames.org/  **Source table download**: http://www.genenames.org/cgi-bin/download  **Place to Explore Table** : https://lforms-service.nlm.nih.gov/apidoc/genes/v1/doc.html    **Description:** The HGNC gene table carries the gene ID, gene symbol and full gene name. The GENE ID is specific to the species. The gene symbol and name is shared by all species with the same gene.    The HGNC-Symb table carries only human genes. The code for this coding system is the HGNC gene code, the "name" or print string is the HGNC gene symbol. More than 28,000 human gene symbols and names have been assigned so far, including almost all of the protein coding genes. But close to 10,000 non-protein coding “genes” do not yet have HGNC names. NCBI creates what might be thought of as interim codes but includes many more genes.  The codes from NCBI and from HGNC are pure numbers and can’t be distinguished by their format. The gene codes we propose in this guide and use in our examples and in the LHC form that inputs gene information are all HGNC codes.  **We bring this up to ask balloters -- is this the right choice? Should we distinguish HGNC gene codes from NCBI gene codes with separate and distinct coding systems?**  If the study includes more than one gene, they can all be entered in one OBX, separated by the repeat delimiter. Alternatively they can be entered into separate OBX’s but the content of OBX-4 will have to be unique for each such repeat. We recommend n.1, n.2, n.3 etc. for such repeated variables in the report section which reports gene symbols (See Table 2). |
| 12 | HGVS- Genomic syntax | | **HGVS.g** | 2.16.840.1.113883.6.327 | **Source organization:** Human Genome Variation Society (HGVS)  **Source table information:** <http://varnomen.hgvs.org/bg-material/refseq/#DNAg>  **HGVS validator:** https://mutalyzer.nl/  **Description:** HGVS syntax that describes the variations (mutations) at the genome level (the DNA before it is spliced to remove introns). The genomic syntax statements which can describe simple or structural variants are distinguished by a leading "g." |
| 13 | HGVS- Transcript syntax | | **HGVS.c** | 2.16.840.1.113883.6.328 | **Source organization:** Human Genome Variation Society (HGVS)  **Source table information:** <http://varnomen.hgvs.org/bg-material/refseq/#DNAc>  **HGVS validator:** https://mutalyzer.nl/    **Description:** HGVS syntax that describes variations (mutations) at the transcript (messenger RNA) level. The transcript syntax statements, which can describe simple and complex variants, are distinguished by a leading "c." |
| 14 | HGVS-Protein syntax | | **HGVS.p** | 2.16.840.1.113883.6.329 | **Source organization:** Human Genome Variation Society (HGVS)  **Source table information:** <http://varnomen.hgvs.org/bg-material/refseq/#proteinp>  **HGVS validator:** https://mutalyzer.nl/    **Description:** HGVS syntax that specifies the variations (mutations) at the amino acid level, which are induced by underlying DNA variants. The protein change statements are distinguished by a leading "p." HGVS.p representations will not exist for variants that occur outside of coding regions. |
| 15 | ICD-10-CM | | **I10C** | 2.16.840.1.113883.6.90 | **Source organization:** National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC)  **Source table information:** http://www.cdc.gov/nchs/icd/icd10cm.htm  **Source table download:** http://www.cdc.gov/nchs/icd/icd10cm.htm#icd2016  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/icd10cm/v1/doc.html  **Copyright:** World Health Organization, http://www.who.int/classifications/icd/en/    **Description:** The International Classification of Diseases (ICD) is the classification used to code and classify mortality data from death certificates. The International Classification of Diseases, Clinical Modification (ICD-10-CM) is used to code and classify morbidity data from the inpatient and outpatient records, physician offices, and most National Center for Health Statistics (NCHS) surveys.  The ICD-10-CM is used to code and classify mortality data from death certificates, having replaced ICD-9 for this purpose as of January 1, 1999. ICD-10-CM is the replacement for ICD-9-CM, volumes 1 and 2, effective October 1, 2015, but of course, decades of ICD-9 data recorded before 2015 will be in medical record systems for a long long time.  The codes are an alphanumeric string. The name is a diagnosis, symptom or other clinical concepts. Some of these codes can be related in a shallow hierarchy. ICD-10-CM codes are 7 digits: digit 1 is alpha; digit 2 is numeric; digits 3–7 are alpha or numeric; and a decimal/dot is placed after the third character. ICD-10-CM includes extensive Combination Codes to better capture complexity.  NCHS, which is part of the U.S. Centers for Disease Control and Prevention (CDC), serves as the World Health Organization (WHO) Collaborating Center for the Family of International Classifications for North America and in this capacity is responsible for coordination of all official disease classification activities in the United States relating to the ICD and its use, interpretation, and periodic revision. |
| 16 | ICD-9-CM | | **I9CDX** | 2.16.840.1.113883.6.103 | **Source organization:** National Center for Health Statistics (NCHS)  **Source table information:** http://www.cdc.gov/nchs/icd/icd9.htm  **Source table download:** http://www.cdc.gov/nchs/icd/icd9cm.htm  **Place to Explore Table :** Not yet implemented <https://www.cms.gov/medicare/coding/ICD9providerdiagnosticcodes/codes.html>  **Copyright:** World Health Organization, http://www.who.int/classifications/icd/en/    **Description:** The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is a subset of ICD-9. ICD-9-CM is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States. The ICD-9 was used to code and classify mortality data from death certificates until 1999, when use of ICD-10 for mortality coding started.    Most ICD-9-CM codes are purely numeric consisting of 3 digits followed by a dot and one or more digits. A select subset start with the letter E or V followed by a number. ICD-9-CM codes are 3-5 digits. This subset of ICD-9 carries only diagnostic codes (the surgical and other procedure codes are excluded). |
| 17 | International System for Human Cytogenetic Nomenclature (ISCN) | | **ISCN** | 2.16.840.1.113883.6.299 | **Source organization:** The International System for Human Cytogenetic Nomenclature (ISCN)  **Source table information:** https://www.karger.com/Article/FullText/353118  **Description:** Like HGVS, The International System for Human Cytogenetic Nomenclature (ISCN) is a syntax. It came out of cytopathology and deals with reporting karyotypes down to the chromosome fusions and many types of small copy number variants.  The full syntax is described in: ISCN (2013): An International System for Human Cytogenetic Nomenclature, L.G. Shaffer, J McGowan-Jordan, M. Schmid (eds). S. Karger, Basel 2013 |
| 18 | Logical Observation Identifier Names and Codes (LOINC)® | | **LN** | 2.16.840.1.113883.6.1 | **Source organization:** Regenstrief Institute |
| S**ource table information:** http://loinc.org/background |
| **Source table download:** http://loinc.org/downloads |
| **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/loinc/v1/doc.html |
| **Copyright:** Regenstrief Institute, http://loinc.org/terms-of-use |
|  |
| **Description:** Logical Observation Identifiers Names and Codes (LOINC®) provides a set of universal codes and names for identifying laboratory and other clinical observations. One of the main goals of LOINC is to facilitate the exchange and pooling of results for clinical care, outcomes management, and research. LOINC was initiated by Regenstrief Institute research scientists who continue to develop it with the collaboration of the LOINC Committee. |
| 19 | Locus Reference Genomic (LRG) | | **LRG-RefSeq** | 2.16.840.1.113883.6.337 | **Source organization:** Locus Reference Genomic (LRG)  **Source table information:** http://www.lrg-sequence.org/about  **Source table download:** http://www.lrg-sequence.org/downloads  **Place to Explore Table :** not implemented    **Description:** LRG is a manually curated record that contains stable, and thus un-versioned, reference sequences designed specifically for reporting sequence variants with clinical implications.  It provides a genomic DNA sequence representation of a single gene that is idealized, has a permanent ID (with no versioning), and core content that never changes. Their database includes maps to NCBI, Ensembl and UCSC reference sequences.    It contained sequences for a total of 1073 genes as of April 2016, with identifiers of the form: "LRG\_####", where #### can be from 1 to N, and N is the last gene processed.  See PMIDs: 24285302, 20398331, and 20428090 for more information. |
| 20 | NCBI MedGen disease subset | **MedGen-Dis** | | 2.16.840.1.113883.6.333 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information:** http://www.ncbi.nlm.nih.gov/medgen/  **Source table download:** ftp://ftp.ncbi.nlm.nih.gov/pub/medgen/  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/disease\_names/v1/doc.html    **Description:** MedGen-disease is a subset of disease concepts (about 20,000 as of January 2016) taken from the NCBI’s MedGen table. It includes most known genetic and clinical diseases.    It drew its content from the NIH Genetic Testing Registry (GTR®), UMLS, HPO, OMIM, Orphanet, ClinVar and other sources, and is probably the most complete compendium of genetic diseases, though it also includes most common clinical diseases. It uses UMLS IDs when they exist and its own ID when not, and links to SNOMED CT and other disease identifiers. The MedGen database includes the inheritance and clinical features of each disease, as well as the map location of underlying genetic basis. |
| 21 | NCBI - genomic and chromosome reference sequences | | **RefSeq-G** | 2.16.840.1.113883.6.330 | **Source organization:** National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine (NLM)  **Source table information:** http://www.ncbi.nlm.nih.gov/refseq/  **Source table download:** ftp://ftp.ncbi.nih.gov/refseq/H\_sapiens/RefSeqGene/  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/refseqs/v1/doc.html    **Description:** Subset of NCBI Human RefSeqs with prefix of NC\_ or NG\_.  Those prefixed with "NC\_" represent the whole genomic RefSeq for individual chromosomes. Those prefixed with "NG\_" represent genes with all of their introns and flanking regions and other larger or smaller genomic sequences.  These are available separately in the NCBI source data file, which includes all human RefSeqs (including those with prefix of NR\_ or XM\_): <ftp://ftp.ncbi.nlm.nih.gov/genomes/Homo_sapiens/ARCHIVE/BUILD.37.3/GFF/ref_GRCh37.p5_top_level.gff3.gz> |
| 22 | NCBI - protein reference sequence | | **RefSeq-P** | 2.16.840.1.113883.6.331 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information:** http://www.ncbi.nlm.nih.gov/refseq/  **Source table download:** ftp://ftp.ncbi.nlm.nih.gov/refseq/release/  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/refseqs/v1/doc.html    **Description:** Subset of NCBI RefSeqs that represent reference sequences for proteins. Not routinely included in reports because Amino acid changes can be computed directly from DNA changes based on transcript reference sequence. However some fields are interested only in the protein sequence change, and proteins can be sequenced independently of DNA sequencing.  We will explore the creation of coding systems for other protein reference identifiers such as UniProtKB accession numbers (<http://www.uniprot.org/help/uniprotkb>**).** |
| 23 | NCBI-transcript reference sequences (RefSeq) | | **RefSeq-T** | 2.16.840.1.113883.6.332 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information:** http://www.ncbi.nlm.nih.gov/refseq/  **Source table download:** ftp://ftp.ncbi.nlm.nih.gov/refseq/release/  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/refseqs/v1/doc.html    **Description:** Subset of NLM RefSeq records with prefix of "NM\_" are reference sequences that represent messenger RNA. |
| 24 | RxTerms-Ingredients Subset | | **RxT-Ingrd** | 2.16.840.1.113883.6.334 | **Source organization:** National Center for Biotechnology Information (NCBI)  **Source table information:**  https://wwwcf.nlm.nih.gov/umlslicense/rxtermApp/rxTermFileStructure.cfm  https://mor.nlm.nih.gov/RxMix/  **Source table download:** https://wwwcf.nlm.nih.gov/umlslicense/rxtermApp/rxTermCondition.cfm  **Place to Explore Table :** https://lforms-service.nlm.nih.gov/apidoc/drug\_ingredients/v1/doc.html    **Description:** RxT-Ingrd is a specialization of the RxNorm database that includes the ingredients in RxTerms (derived from RxNorm) except allergens (used for allergy testing), combination ingredients, and inactive ingredients. The subset is designed for identifying drugs that might be the focus of pharmacogenetic testing. |
| 25 | SNOMED-CT | **SCT** | | 2.16.840.1.113883.6.96 | **Source organization**: International Health Terminology Standards Development Organisation  **Source table information:** http://www.ihtsdo.org/snomed-ct  **Source table download:** <https://www.nlm.nih.gov/healthit/snomedct/us_edition.html> (requires free UMLS License)  **Place to Explore Table :** Not implemented in the LHC public site, but registered users (with free UMLS license) can browse SNOMED CT via: <https://www.nlm.nih.gov/research/umls/Snomed/snomed_browsers.html>  **Copyright:** International Health Terminology Standards Development Organisation, http://www.ihtsdo.org/snomed-ct/get-snomed-ct    **Description:** SNOMED CT is a concept-based, scientifically validated terminology that provides a unique and permanent concept identifier that can be included in multiple HL7 data types, including CD and CE. If the concept is found to be ambiguous or the meaning changes, the concept is inactivated but still retained and the identifier is never reused. It is required by Meaningful Use for many purposes. SNOMED CT's concepts are interrelated hierarchically and use description logic.  SNOMED CT code development is in process for the answer lists in this guide, and in the meantime only LOINC answer codes are available. | |
| 26 | Unified Code for Units of Measure (UCUM) | | **UCUM** | 2.16.840.1.113883.6.8 | **Source organization:** Regenstrief Institute  **HL7 Long Name:** Unified Code for Units of Measure  **Source table information:** http://unitsofmeasure.org/trac  **Source table download (common UCUM units in clinical care):** https://loinc.org/usage/units  **UCUM validator and converter :** https://lhncbc.github.io/ucum-lhc/    **Description:** Unified Code for Units of Measure (UCUM) is a syntax for defining units of measure including both metric and conventional units. It comes with tables and software for validating and converting values expressed in one unit of measure to a different but commensurate unit of measure. Its purpose is to facilitate unambiguous electronic communication of quantities together with their units.  UCUM codes are intended for computer use. In HL7 V2, traditional unit strings can be included along with UCUM as needed.  UCUM defines a syntax; so, like HGVS, there is no numeric code attached and no table with a complete enumeration. However, NLM and Regenstrief Institute developed a table of common UCUM units used in clinical care, available at: <https://loinc.org/usage/units>.  Lister Hill Center at NLM has also developed a JavaScript program to convert and validate UCUM units, available at: https://lhncbc.github.io/ucum-lhc/. |

## Use of OIDs for Other Coding Systems

While discussing this subject, we wish to point out a mechanism for reporting genomic identifiers for reference sequences and variants from *public* databases that are not listed in Table 1 or HL7’s V2 table 0396 or the HL7 OID registry. Let’s consider the recording of such a transcript reference ID as the value of LOINC #51958-7, *Transcript reference* *sequence* (See Row B.3 in Table 2 as an example). You would store the ID for the reference sequence from that public source in CWE.1 and that source’s OID in CWE.14. The same approach could be used for other genomic identifiers including genetic variation IDs, genomic reference sequence IDs, etc., that came from public sources not registered in HL7 Table 0396 or the HL7 OID registry. Having said that, we encourage you to request an HL7 OID and a coding system name for that source’s genomic table from HL7 so that the identifiers for that source could be treated like all of the other coding systems used in this guide: If you did, the code value would go into CWE.1 and the HL7 coding system name (from HL7 Table 0396 or from the HL7 v2 linkage name in the HL7 OID table) in CWE.3 and in this case CWE.14 would stay empty.

This same OID mechanism *could* be used for identifying source tables for genomic identifiers from private databases, but that would defeat the effort to standardize genetic information to which this guide is dedicated. So we strongly encourage the submission of new variations and other genomic content to public registries such as NCBI or Ensembl, instead of, or in addition to, only keeping that data in a private database. In the medium term, we expect that genetic testers will be able to obtain unique, public identifiers quickly for all new variants they find, thus diminishing or reducing the need for alternate registries.

# Models of this V2 Genetics reporting message

Figure 1 is a model of the clinical genetics report message showing all of the major LOINC panels that can make up a report and how they are related. To keep it simple, this model does not show the few single observations that may repeat within a panel



Figure 1: Object model of elements contained within the Coded Clinical Genomics Results Lite Message

We also modeled this specification as an input form using LHC-Forms,[[1]](#footnote-2) a web-based JavaScript widget which we instantiated with all of the LOINC codes and their attributes, so users could test the specification with real data and decide which of the variables in the full specification they want to use. LHC-Forms will also produce example HL7 messages showing the payload that a user entered we used this capability (with some hand editing) to create the examples of genetic messages for this specification at the end of this guide (See Section 6).

You can use LHC-Forms at <https://lforms-demo.nlm.nih.gov/>. (See Figure 2) This widget will let you choose between NCBI and COSMIC identifiers for a few types of variables. In most cases LHC-Forms assumes a default coding system for each variable, but V2 message implementers are free to insert the other coding systems associated with a given LOINC code in tables 2 through 6 when they construct their messages directly. Figure 2 shows some of the ten fields that are auto-populated when you choose a variation registered in ClinVar.

A related LHC open source JavaScript tool for validating and converting UCUM units may also be of interest to this audience and is available at <https://lhncbc.github.io/ucum-lhc/> .

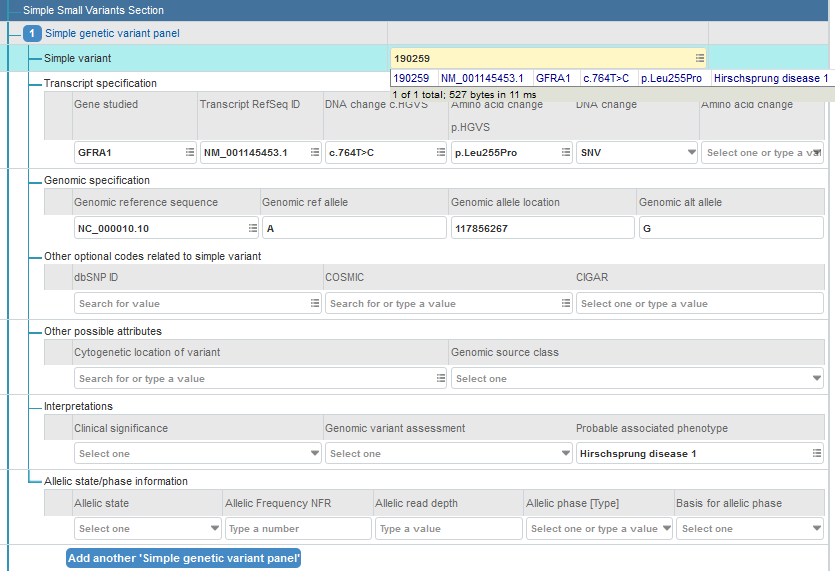


Figure 2: Screenshot of LHC-Forms widget for this specification

Showing input fields for Simple Variants. All except the first field (simple variant) were auto-populated from the ClinVar table.

# Clinical message definitions with built in examples (in Table 2 through Table 6)

## OVERVIEW

The set of closely related tables below (Table 2 through Table 6) together carry all of the LOINC codes (variables) that can be used in this specification. They define the message structure and are organized in the form of an example “message”. Each table describes one section of a clinical genomics report as is described in Section 5.4.

In the first column of these tables, we have inserted short alphanumeric labels (e.g. A, A.1, A.2, etc.) to provide an easy way to reference specific content in this table. These labels have no meaning outside of this document, and have no role in HL7 messaging.

## How example message content and LOINC usage rules are combined in this table

To make it easier for readers to interpret the LOINC codes and how they are organized, each row in Table 2 through Table 6 corresponds to an OBX segment with example content for OBX-2, OBX-3.1 OBX 3.2, OBX-4 and OBX-5 that is appropriate to that row’s LOINC code. For easy readability, these pseudo OBX’s carry their values in table columns rather than as delimited text as one would see in a real message. (In Section 6 we also present a series of example Coded Clinical Genomics Lite messages in standard HL7 delimited text.)

Table 2 through Table 6 also contain fields that carry information about the LOINC term itself: its optionality, its cardinality, narrative text that explains the term and how to use it, and for terms with coded answers either its answer list or coding systems. Please note: the R/O/C and cardinality listed here are LOINC attributes that describe the “requiredness” of a LOINC term within a panel. They have no relationship to the field requirements in HL7. LOINC cardinality indicates whether the term is required and how many repeats are permitted. For example, optional with no upper bound is displayed as “0..\*” and required but not permitted to repeat is displayed as “1..1”. So most of the information about a LOINC term is integrated into the same row that carries example data. More information about each coding system cited in Table 2 through Table 6 can be found in Table 1 with coding systems ordered by HL7 V2 linkage name value from the HL7 Vocabulary Table (0396).

## Conventions for row labels in the nested and repeating panels of the example/definition tables

Because we are using this table to exemplify a full message, some groups of rows repeat in groups as they would in real messages. In the LOINC database, each such group is defined as a panel and the panel and its attributes are included in the table to provide the cardinality structure to the table. However, these LOINC panel IDs are not included in the message as OBRs as they were in the 2013 HL7 Clinical Genomics Guide. Instead, this version uses OBX-4 to define the hierarchy. For example, the LOINC terms from panel describing the simple variation will repeat as many times as there are simple variations to report; the same applies to structural, pharmacogenomics and complex variations. The pharmacogenomic part of the example table (Table 5) illustrates this well. It includes a pharmacogenomics panel (LOINC #82118-1) at row D1 followed by two other instances. The terms for the first panel instance appear in the rows labeled D1, D1.1, D1.2; the second and third instances are labeled D2, D2.1, etc. and D3, D3.1, D3.2, etc., respectively. The first two of these panels include child panels titled (medication usage panel (LOINC 82117-3) that provide guidance about the use of a named drug considering the variations reported in their parent panels. The variables in the first such panel, under D1, are labeled E1, E1.1, E1.2, etc. The variables in the next two instances of these panels under D1 follow the same pattern (i.e., E.2, E2.1, E2.2, etc. and E3, E3.1, E3.2, etc.). The guidance panels under the second pharmacogenomic panel, starting at Row D2 have row labels following the same pattern as those under D1. Remember that these labels are ONLY used for referencing row content in this guide and have no role in the HL7 message.

In the Tables, in repeated instances of the same LOINC term, we do not include the LOINC term’s sometimes bulky description and answer lists. Instead we include a pointer to the previous row that carries that content using the row label to identify it.

## Overview of the five different possible sections of a clinical genetics report

Conceptually this set of tables is one table, but we broke it into five separate tables so it would be more manageable and correspond to the five different kinds of content found in the five different sections of a V2 clinical genetics report. Within a given report section, the example content will represent a single consistent real world result. Across sections they may not.

Report sections 1 through 3 (tables 2 through 4) are comprised of a single panel and all of the rows within any such panel begin with the same letter, A, B or C respectively. Although the HL7 message will not contain nested OBR sections, we include the LOINC panels to enhance understanding of the relationship of the content and to show the hierarchical relationship among the groups of observables in these tables, which the OBX-4 dot notation will follow. . Report sections 4 and 5 -- Pharmacogenomics and Complex variants -- contain nested LOINC panels and the rows within these different panels begin with different letters i.e. “D” and “E” or “F” and “A”, for pharmacogenomics and complex variants respectively. Remember these row labels are not codes – they are merely a convenient way to reference the tables for the discussions in this guide, not a formal part of the standard or the message

* **Variables that Apply to the Overall Study: Report section 1**

The first section carries the observations that would apply overall to a report. Some of these observations carry detailed technical content, such as the version number for the SNP codes in the report, the set of mutations sought in targeted mutation study, overall impression, and a copy of the whole report as delivered traditionally. We expect that some content from this first section would be part of almost every clinical genetics report message. The other four sections are more specialized and we would usually expect only one or two of them in addition to the overall results in report section 1. (See Table 2.)

* **Simple Variants: Report section 2**

The second section reports simple genetic variation which do not act together to define a single phenotype. The rows for the simple variant have labels beginning with “B”. All of the variables in this section are part of one large panel, (LOINC #81250-3) the simple variant panel. This panel includes 24 variables, but most laboratories will use only 4-6 of them.

Of note in this section is LOINC #69548-6 –“genetic assessment of variant”-- row B18. Most genetic reporting of negatives is by default. The front of the report describes what was tested for – either a list of discrete variants or regions of the genome that were sequenced -- and the results call out only the “abnormal” variations found. LOINC 69548-6 is the term that enables statement about all loci whether normal or not, and carries “no call” as one of its answers. So reporters can specify whether each locus examined was “normal” or “abnormal”.

This report section also includes a variable for reporting the phase of each variant (Row B.23) and the kind of evidence used to decide the phase (Row B.24). (See Table 3.)

* **Structural Variants: Report section 3**

The third section is dedicated to structural and copy number variations -- the kind that one would find in NCBI’s dbVar or in COSMIC’s structural variant files. These focus on structural variants with imprecise break points. Those with precise break points may be reported in the report section 2 if they are registered in ClinVar or a comparable public database. All of the rows in this section carry labels beginning with C and are part of a LOINC panel which can repeat depending on the number of structural variants reported. (See Table 4.)

* **Pharmacogenomics: Report section 4**

The fourth section is dedicated to pharmacogenomic test reporting. It includes two panels. The first panel, whose rows labels all begin with D, and repeat for each gene or gene pair with mutations that would influence drug metabolism or efficacy. The second panel, nested inside of the first, (whose row labels begin with E) provides guidance about adjustment for drugs whose actions (e.g. metabolism or efficacy) might be influenced by the mutations reported in the parent panel. These panels repeat per drug about which there is guidance within a given D panels. In some cases the laboratory will only provide guidance about the drugs about which the ordering provider inquired, and in other cases, the laboratory reports this information about all common drugs.

This report section includes a cross linkage term that enables pharmacogenomic reports to include all the details about individual mutations that add up to the genotype. These can be from Section 2, 3 or 5. This example includes multiple genotypes and multiple drug guidance statements for each of them. (See Table 5 and additional details in Section 1.3.3).

* **Complex Variants: Report section 5**

Section 5, where all of the row labels begin with F or G, also includes nested panels. This section is for complex variants, which are those for which many simple mutations taken together have one effect or phenotype. Haplotypes are one of the most common complex variants. (See Table 6.). The reason for this section is to provide a way to report something about a set of variants that together have a special meaning and to list the individual variation in question. When the report recipients need only HGVS representation of the complex variant and no further genetic details about the component variation, this section is not really needed.

### Variables that apply to the OVERALL study: report section 1 (Table 2)

Table 2: Report Section 1 for Variables that Apply to the Overall Study

|  | **OBX-2** | **OBX3.1** | **OBX3.2** | **OBX-4** | **OBX-5** | **LOINC Panel/Definitional terms** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Label** | **Type** | **LOINC #** | **LOINC name** | **Sub ID** | **Example values** | **R** | **Cardinality** | **Term description** |
| Top | N/A | **81247-9** | **Master HL7 genetic variant reporting panel** |  |  |  | 1..1 | This panel term provides a handle within the LOINC database that holds together all of the terms and panels that are available for use in a V2 Clinical Genomics lite message.  *Because this guide uses the OBX-4 to organize the hierarchy of “records” in the message (see details in Section 1.3.3), the LOINC codes for panels after the master panel will not appear as OBRs in the message as was the case in the*  2013 HL7 *clinical genomics message.*  All of the genomic data reported in this panel uses a coordinate system beginning with 1, and assumes the variants are reported from the positive strand. This is the assumption embedded in HGVS, the public distribution of NCBI, Ensembl, COSMIC, and most other genomic databases. This choice does not constrain receivers from converting to a different (e.g. 0 to start) coordinate system. It only specifies what goes in the message. |
| **l** | **Report section 1** | | | | | | | |
| A | Panel | 81306-3 | Variables that apply to the overall study | NA | NA |  | 1..1 |  |
| A.1 | TX | [53577-3](http://s.details.loinc.org/LOINC/53577-3.html) | Reason for study | 1 | “Worried about family planning” | O | 0..1 | HL7 provides OBR-31 for recoding the reason for the study. The LOINC code is included in this panel for convenience of form definition, because it is often captured in a form with this variable. But ideally, in a lab message it should be delivered in HL7 OBR-31. |
| A.2 | CWE | [51967-8](http://s.details.loinc.org/LOINC/51967-8.html) | Genetic disease(s) assessed | 1 | 2971795010^Deficiency of isobutyryl-coenzyme A dehydrogenase (disorder)^SCT | C | 0..\* | **Coding systems:**   1. **SCT** 2. **I9CDX** 3. **I10C** 4. **MedGen-Dis**   Applies only to studies that target a disease.  MedGen, from NCBI, carries more than 20,000 genetic diseases taken from NLM’s Unified Medical Language system (UMLS®), the NIH Genetic Testing Registry (GTR®), UMLS, HPO, OMIM, Orphanet, ClinVar, and their codes link to SNOMED codes when available.  It will be up to the message generator to specify the coding system within the message. We encourage the use of SNOMED CT in this field, and the example values shown in the OBX-5 column use SNOMED CT Codes as the coding system because it is the preferred direction in the US. However, the LHC-forms demo of this draft specification shows the content from NCBI MedGen, because it is the most complete with respect to genetic diseases, the public can access it without a password worldwide, and it includes mappings to SNOMED CT. Any or all of the above coding systems could be used in the message. |
| A.3 | CWE | 51963-7 | Medications assessed [Nom] | 1.1 | 50005^Fluoxetine^RxT-Ingrd~ 84701^Atorvastatin^RxT-Ingrd~   45000^Naproxen^RxT-Ingrd~ 11289^Coumadin^RxT-Ingrd | C | 0..\* | **Coding system: RxT-Ingrd**  Applies only to pharmacogenomics studies. Carries the medications for which there is concern that genetic variation might influence the efficacy and/or the rate of metabolism.  This content will usually be an Ask-at-Order-Entry (AOE) question. In a single OBX, repeats can enter multiple medication identifiers separated by repeat delimiters (~) as shown in the example. Alternatively, implementers can send each drug in a separate OBX, but in that case, OBX-4 must be different for each OBX segment (e.g. 1.1, 1.2, 1.3, etc.). |
| A.4 |  | New LOINC | Default transcript reference sequence | 1 |  | O | 0..1 | The full HGVS expression includes a variety of components starting with the reference sequence, but when laboratories report the long list of mutations they are targeting, they usually record just the HGVS.p except when it is a non-coding region in which case they record the HGVS.p notation. They also report a default reference sequence (usually a transcript reference sequence) that applies to the whole list of targeted mutations and, in some cases, the mutations found as well. This variable is included to accommodate that common practice. |
| A.5 | CNE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene(s) assessed [Nom] | 1.1 | 21497^ACAD9^HGNC-Symb | C | 0..\* | **Coding system: HGNC-Symb**  The code for this coding system is the HGNC code for the gene, the print string (name) is the HGNC symbol not the full gene name but the latter can always be retrieved from the HGNC table with the gene ID.  If the study includes more than one gene, they can all be entered in one OBX, separated by the repeat delimiter. Alternatively they can be entered into separate OBX’s but the content of OBX-4 will have to be unique for each such repeat. We use 1.1, 1.2, 1.3 etc. for such repeated variables.  Note we have recorded 1.1 for the OBX-4 values of for variables that *might* repeat individually within their panel  In this guide we focus only on human genetics. (Will address extension to other species in the future). |
| A.6 | CWE | [36908-2](http://s.details.loinc.org/LOINC/36908-2.html) | Gene mutations tested for[Nom] | 1.1 | 7129^NM\_000492.3(CFTR):c.3846G>A (p.Trp1282Ter)^7129^NM\_000492.3(CFTR):c.3846G>A (p.Trp1282Ter)^CLINVAR~ 38799^NM\_000492.3(CFTR):c.489+1G>T^ 38799^NM\_000492.3(CFTR):c.489+1G>T^ClinVar-V | C | 0..\* | The list of gene mutations tested for is required if the study is a targeted mutation analysis (i.e. either a study for known family mutations, or for a fixed set of mutations offered by the laboratory). Because laboratories will routinely report on only a subset of the mutations included in a gene chip, the identification of the gene chip alone is not enough.  These are most often reported as HGVS.p mutations in narrative reports and in usual narrative reports do not include full details such as the reference sequence. If multiple genes are reported, the HGVS expression should include the gene name.  Multiple mutations can be entered in one OBX-5 separated by repeat delimiters. Alternatively they can each be reported in a separate OBX. In that case OBX-4 should be different for each such OBX, specifically 1.1, 1.2, 1.3, etc.  Note: we have recorded 1.1 for the OBX-4 values for variables that *might* repeat individually within their panel. |
| A.7 | NR | 51959-5 | Ranges of DNA sequence examined | 1.1 | 2000753^2234579 | C | 0..\* | Preferred if the method is a sequencing study. The first value of the numeric range defines the start location, the second value defines the end location of the Sequence. We recognize that this information may be proprietary and is often not revealed.  The locations are specified to the associated Genomic reference sequence, and may repeat if the range is discontinuous. At present in HL7 V2 each repeat of an NR requires a separate OBX, and the OBX-4 values will have to differ among such repeats. We recommend 1.1, 1.2, 1.3 etc.  **Ballot Note -- NR data types are supported by HL7 V2, but not yet supported by the LRI lab specification. We have asked that NR be allowed in that spec and to allow repeated NR values in one OBX-5 as will be allowed in LRI for coded data types.**  Note: we have recorded 1.1 for the OBX-4 values of for variables that *might* repeat individually within their panel**.** |
| A.8 | TX | 81293-3 | Description of ranges of DNA sequences examined | 1 | “All coding regions and appropriate flanking regions “ | C | 0..1 | Genetic test reports only rarely include explicit numeric ranges (as row A.8 could carry) because they are often proprietary. So reports tend to describe the regions in narrative (e.g. “all coding regions and appropriate flanking regions”). This variable is included to capture such descriptions. It is only relevant to sequencing studies. Either this code or LOINC #51959-5 should be included when reporting structural variants. |
|  |  |  | **Summary results** |  |  |  | | |
| A.9 | CNE | [51968-6](http://s.details.loinc.org/LOINC/51968-6.html) | Discrete variation analysis overall interpretation | 1 | LA6576-8^Positive^LN | R | 1..1 | **Answer List: LL541-4**   |  |  | | --- | --- | | 1. **Positive** | **LA6576-8** | | 1. **Negative** | **LA6577-6** | | 1. **Inconclusive** | **LA9663-1** | | 1. **Failure** | **LA9664-9** |   Reported when mutation analysis (sequencing or targeted mutations) is done.  Provides a coarse *overall* interpretation of the results reported. More detailed interpretations are also associated with each distinct reported variant below. |
| A.10 | CWE | NEW LOINC | Deletion-duplication overall interpretation | 1 | LAxxx^No deletion duplications detected in studied regions^LN | C |  | **Only reported when deletion/duplication studies performed.**  **Answer list (Tentative/Codes Pending)**   1. **No deletion duplications detected in studied  regions** 2. **Positive for deletion duplications** 3. **Inconclusive** |
| A.11 | FT;  ED | 51969-4 | Full narrative report  *(e.g. PDF, Word Document that would look like current reports)* | 1 | Example pending | O | 0..1 | This attribute can carry the full narrative report in two different data types, e.g. FT=Formatted text or as ED=encapsulated data which can accommodate Word DOCs, PDFs and other special media types.  In most cases these will be full reports with page headers and footers, similar or identical to the existing “paper” report. But this could be just narrative text to complement the other structured data delivered.  If this content is not reported as the simple formatted text, follow HL7 V2 specifications for recording the media type and other attributes of an HL7 encapsulated data type. |
|  |  |  | **Technical details** |  |  |  | | |
| A.12 | CWE | 62374-4 | Human reference sequence assembly [nom] | 1 | LA14029-5^GRCh37^LN | C | 0..1 | **Answer List: LL1040-6**   |  |  | | --- | --- | | 1. **NCBI35** | **Answer code pending** | | 1. **NCBI36** | **Answer code pending** | | 1. **GRCh37** | **LA14029-5** | | 1. **GRCh38** | **Answer code pending** |   May or may not be needed depending on the reference sequences to which the results are anchored. It is not needed for transcript reference sequences nor for NCBI genomic reference sequences when they include version numbers (the numbers after the dots). It is needed for genomic reference sequences if they lack the version number and for Ensembl genomic and chromosome reference sequences when the build is not part of the mutation name.  We include only one slot for the assembly build in the overall report section, assuming that it applies to all repeated variations. |
| A.13 | ST | 81303-0 | HGVS version [ID] | 1 | 2.120831 | O | 0..1 | HGVS now gives new version numbers when its recommendations change. These were previously based on the date of the change. So if the change date was 2012-08-31. The version of the HGVS version would be specified as 2.120831. However, we’ve since noticed the most recent version is labeled 15.11. **Balloters please tell us the correct way to represent HGVS versions.**  (HGVS nomenclature version 15.11 is described in Den Dunnen et al. (2016) HGVS recommendations for the description of sequence variants: 2016 update. Hum. Mutat. 25: 37: 564-569.)  Note: The reporting of the HGVS version identification in genetics reports is rare today. |
| A.14 | NM | 82115-7 | dbSNP version [ID] | 1 | 137 | O | 0..1 | **As of summer 2016, dbSNP builds number from 1 to 147 – the first done on December 1, 1998, and the most recent on April 14, 2016.**  **Details can be obtained from NCBI at**  <http://www.ncbi.nlm.nih.gov/projects/SNP/buildhistory.cgi>  dbSNP version changes are only made to correct errors. The version # does not change the meaning of the dbSNP RS # per se, but may change the value of the location number in relation to the build. |

### Simple Variants: Report section 2 (Table 3)

Table 3: Report Section 2 for Variables that Define a Simple Variant (could be more than one simple variant not related to each other)

|  | **OBX-2** | **OBX 3.1** | **OBX 3.2** | **OBX-4** | **OBX-5** | **LOINC Panel/Definitional terms** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Label** | **Type** | **LOINC #** | **LOINC Name** | **Sub ID** | **Example values** | **R** | **Card** | **Term description** |
| B | N/A | **81250-3** | **Simple genetic variant panel** |  | Does not carry values |  | 0..\* | **Repeats for each simple variant reported.**  This panel code does not carry values in its OBX-5 It provides a handle for holding all of the LOINC term needed to define a simple variation.  It will not be included in the message if we continue to use OBX-4 content to define the hierarchy rather than nested OBRs and OBX’s |
| B.1 | CWE | 81252-9 | Simple genetic variant | 2.1 | 30880^NM\_014049.4(ACAD9):c.1249C>T (p.Arg417Cys)^CLINVAR-V | C | 0..1 | **Coding systems:**   1. **CLINVAR-V** 2. **COSMIC-Smpl**   Ideally, the code for the genetic variant is the ID specified for that variant in the same public database. The name (print text) is that given by the public database—usually a combination of attributes (e.g. the RefSeq, gene symbol, c.HGVS etc.). The public database is identified by the coding system name from HL7 Table 0396 (or the V2 link name in the OID table) in CWE.3. See Table 1 for a list of all of the coding systems used in this guide.  If the variant has been registered in COSMIC or ClinVar, many of the following attributes can be automatically pulled from the public database and loaded into separate LOINC terms (see those that follow this panel). Until a value is available from a stable public allele registry, fillers can enter these attributes in the OBXs specified by the terms that follow.  Efforts are underway to establish a global unique identifier for each allele; so additional coding systems may appear in future versions of this guide. Plus there are ongoing discussions of creating an allele registry to provide standard IDs quickly for new sequences.  At the very least, either the simple variant in row B.1 with its code and name or all of the variables in rows B.2 to B.5 should be included in the message. |
| **Transcript Specification (Separate observations for each of the components of the simple genetic variant name)** | | | | | | | | |
| B.2 | CWE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene studied [ID] | 2.1 | 21497^ACAD9^HGNC-Symb | C | 0..1 | **Coding system: HGNC-Symb**  When applicable, this variable identifies the gene on which the variant is located. The code is the HGNC code for the gene, the print string (name) is the HGNC symbol**.** The gene identifier is also carried in the transcript reference sequence database; so the gene information tends to be redundant but is usually reported explicitly. |
| B.3 | CWE | 51958-7 | Transcript Reference Sequence ID | 2.1 | NM\_014049.4^ NM\_014049.4^ RefSeq-T | C | 0..1 | **Coding system choices:**   1. **RefSeq-T** 2. **Ensembl-T** 3. **LRG**   At least one of the transcript or genomic reference sequence (rows B.8-B.11) must be included. If the HGVS.c is included, the transcript reference sequence must be included. |
| B.4 | CWE | 48004-6 | DNA change cHGVS | 2.1 | c.1249C>T^ c.1249C>T ^HGVS.c | C | 0..1 | **Coding system: HGVS.c**  HGVS specification of the change at the DNA level relative to the transcript RefSeq. |
| B.5 | CWE | [48005-3](http://s.details.loinc.org/LOINC/48005-3.html) | Amino acid change pHGVS | 2.1 | p.Arg417Cys^ p.Arg417Cys ^HGVS.p | C | 0..1 | **Coding system: HGVS.p**  HGVS specification of the change at the amino acid (protein) level caused by the DNA change. If the change is in a non-coding region, this variable will not be reported. HGVS recommends that amino acid changes never be reported without also reporting the DNA change. |
| B.6 | CWE | 48019-4 | DNA change [type] | 2.1 | LA6690-7^Substitution^LN | O | 0..1 | **Answer List : LL379-9**   |  |  | | --- | --- | | 1. **Wild Type** | **LA9658-1** | | 1. **Deletion** | **LA6692-3** | | 1. **Duplication** | **LA6686-5** | | 1. **Insertion** | **LA6687-3** | | 1. **Insertion/Deletion** | **LA6688-1** | | 1. **Inversion** | **LA6689-9** | | 1. **Substitution** | **LA6690-7** |   Type of DNA variation reported. Taken from: 2013 HL7 V2 Clinical Genomics Implementation Guide.  See also HGVS DNA variant descriptions. <http://varnomen.hgvs.org/> |
| B.7 | CWE | 48006-1 | Amino acid change [type] | 2.1 | LA6698-0^Missense^LN | O | 0..1 | **Answer List: LL380-7**   |  |  | | --- | --- | | 1. **Wild Type** | **LA9658-1** | | 1. **Deletion** | **LA6692-3** | | 1. **Duplication** | **LA6686-5** | | 1. **Frameshift** | **LA6694-9** | | 1. **Initiating Methionine** | **LA6695-6** | | 1. **Insertion** | **LA6687-3** | | 1. **Insertion and Deletion** | **LA9659-9** | | 1. **Missense** | **LA6698-0** | | 1. **Nonsense** | **LA6699-8** | | 1. **Silent** | **LA6700-4** | | 1. **Stop Codon Mutation** | **LA6701-2** |   Type of amino acid change reported. Taken from: 2013 HL7 V2 Clinical Genomics Implementation Guide.  See also <http://www.hgvs.org/mutnomen/recs-prot.html> |
|  |  |  | **Genomic Specification—a VCF like organization** | | | | | |
| B.8 | CWE | 48013-7 | Genomic Reference Sequence [ID] | 2.1 | NG\_017064.1^ NG\_017064.1^RefSeq-G | C | 0..1 | **Coding system choices:**   1. **RefSeq-G** 2. **Ensembl-G**   If the genomic specification is given, then this and the following 3 terms must be presented (i.e. LOINC# 69547-8 (Row B.9), 81254-5 (Row B.10) and 69551 (Row B.11)). |
| B.9 | ST | [69547-8](http://s.details.loinc.org/LOINC/69547-8.html) | Genomic Ref allele | 2.1 | C | C | 0..1 | The DNA string in the reference sequence (Ref Allele) with which the DNA string in the test sample differs, starting at the first position given in LOINC# 81254-5’s Genome Allele location. |
| B.10 | NR | 81254-5 | Genomic Allele start-end | 2.1 | 31731^31731 | C | 0..1 | The beginning and end of the Ref Allele that was replaced by the Alt Allele. The beginning is counted as the first position in the genomic reference showing a contiguous set of base changes in the sample DNA being tested. The end is the comparable last position. |
| B.11 | ST | [69551-0](http://s.details.loinc.org/LOINC/69551-0.html) | Genomic Alt allele | 2.1 | T | C | 0..1 | The DNA sequence in the test sample (Ref Allele) that is different from the DNA sequence in the reference sequence (Ref Allele) –  Note the examples of LOINC#s 69547-8 (Row B.9), 81254-5 (Row B.10) and 69551 (Row B.11) – could also be described in a HGVS.g expression as: g.31731C>T |
|  |  |  | **Other optional codes related to a simple genetic variant** | | | | | |
| B.12 | ID | 81255-2 | dbSNP ID | 2.1 | rs[368949613](http://www.ncbi.nlm.nih.gov/snp/368949613)^ rs[368949613](http://www.ncbi.nlm.nih.gov/snp/368949613)^dbSNP | O | 0..1 | **Coding system: dbSNP**  The “SNP” in NCBI’s dbSNP database name, originally meant Single Nucleotide Polymorphisms (variants), but now is defined to mean “Short Genetic Variation”. (<http://www.ncbi.nlm.nih.gov/books/NBK174586/>)  Each dbSNP is given an ID with a prefix of “rs”. The dbSNP database defines the location and size of the variant, but does not distinguish among different patterns of the same size at the same location. So there would be one rs SNP code for a change of AAA or ACA at the same location, but AAAA at that location would get a different dbSNP code.  DbSNP has versions (see Row A.14 LOINC 82115-7 dbSNP version [ID]), but new versions don’t change the meaning of a dbSNP rs#. Some rs#s may have different locations with respect to the build depending on the version, but only when a change was made to correct an error. The actual meaning of the SNP rs code does not change.  The rs is an identifier for the location of a variant and the type of variant, NOT the allele at that location. Be aware that dbSNP codes cannot stand alone as an identifier -- if you want to use rs to encode a simple genetic variant, the alt allele (LOINC 69551-0) or the full HGVS for the variant must also be specified. |
| B.13 | CWE | 81256-0 | COSMIC-simple genetic variant | 2.1 | Example pending | C | 0..1 | **Coding system: COSMIC-Smpl**  COSMIC (Catalogue of Somatic Mutations in Cancer) is often the preferred code for cancer mutations. The COSMIC simple mutations database carries records that include a specimen ID and mutation ID (HGVS), as well as the organ, histology and other specifics for each submission. The LHC Clinical Table Search Service look up includes only one record per unique mutation ID.  The COSMIC simple variant file has fields that correspond to many of the fields in ClinVar, except that COSMIC uses Ensembl reference sequences and the single letter code for p.HGVS.  COSMIC stores simple mutations and structural mutations in separate tables and this guide provides separate coding systems for each (see structural variants in report section 3). Accordingly we also created distinct LOINC variables for COSMIC simple variants and COSMIC structural variants (see Row C1.9) because COSMIC keeps them in separate databases with different attributes and this aligns with NCBI’s approach. |
| B.14 | CWE Allele | 81257-8 | CIGAR [Nom} | 2.1 |  | O | 0..1 | Used primarily for alignment in earlier stages of genetic study analysis. We have not seen usage in routine clinical reports. |
|  |  |  | **Other possible attributes** | | | | | |
| B.15 | CWE | 48001-2 | Chromosome location of genetic variant | 2.1 | 3q21^3q21^Chrom-Loc | O | 0..1 | **Coding system: Chrom-Loc**  **Description:** Chromosome location (AKA chromosome locus or cytogenetic location), is the standardized syntax for recording the position of genes and large mutations. It consists of three parts: the Chromosome number (e.g. 1-22, X, Y), an indicator of which arm – either “p” for the short or “q” for the long, and then a series of numbers separated by dots that indicate the band, sub band and sub-sub band of the locus (e.g. 2p16.3). There are other conventions for reporting ranges and locations at the ends of the chromosomes.  The table of these chromosome locations was loaded with all of the locations found in NCBI’s ClinVar variation tables. It will expand as additional sources become available. This may not include all finely grained chromosome locations that exist. Users can add to it as needed. We have not found a table of chromosome locations with standard codes. **Balloters: if you know of a publicly available and maintained list of chromosome locations with standard codes please forward to us.** |
| B.16 | CNE | [48002-0](http://s.details.loinc.org/LOINC/48002-0.html) | Genomic source class [Type] | 2.1 | LA6683-2^Germline^LN | O | 0..1 | **Answer List: LL378-1**   |  |  | | --- | --- | | 1. **Germline** | **LA6683-2** | | 1. **Somatic** | **LA6684-0** | | 1. **Prenatal** | **LA10429-1** | | 1. **Likely germline** | **LA18194-3** | | 1. **Likely somatic** | **LA18195-0** | | 1. **Likely prenatal** | **LA18196-8** | | 1. **Unknown genomic origin** 2. **De novo** | **LA18197-6**  NEW |   We associate this variable with the variant so that distinction about the kind of variant can be made when somatic and germline variants will be observed in one study and they have to be distinguished in the report. Answer list taken from NCBI Variation glossary (<http://www.ncbi.nlm.nih.gov/variation/docs/glossary/>). **Balloters -- In the first draft the variables are reported once in the “Variables that apply to the overall report” section (see Table 2). Balloters please comment: should it always be reported per variant?** |
|  |  |  | **Interpretations** | | | | | |
| B.17 | CNE | [53037-8](http://s.details.loinc.org/LOINC/53037-8.html) | Genetic variation clinical significance [Imp] | 2.1 | LA6668-3^Pathogenic^LN | O | 0..1 | **Answer List: LL4034-6**   |  |  | | --- | --- | | 1. **Pathogenic** | **LA6703-8** | | 1. **Likely pathogenic** | **LA6704-6** | | 1. **Uncertain significance** | **LA6705-3** | | 1. **Likely benign** | **LA6706-1** | | 1. **Benign** | **LA6707-9** |   Answer list taken from PMID 25741868 (PMCID: PMC4544753). |
| B.18 | CWE | 69548-6 | Genetic variant assessment [Imp] | 2.1 | LA9633-4^Present^LN | O | 0..1 | **Answer List: LL1971-2**   |  |  | | --- | --- | | 1. **Present** | **LA9633-4** | | 1. **Absent** | **LA9634-2** | | 1. **No call** | **LA18198-4** | | 1. **Indeterminate** | **LA11884-6** |   Most genetic reporting of negatives is by default, the specific mutations (or DNA ranges) tested are reported and only the positives are reported explicitly.  For those who want to report interpretations on a set of specified locations whether normal or not, LOINC 69548-6 is the term that enables this style of reporting, and it includes in its answer list the “no call” option. Thus it permits every examined loci to be described individually as present, absent, (no call), or indeterminate. |
| B.19 |  | 81259-4 | Probable associated phenotype [Imp] | 2.1 | C1970173^ Acyl-CoA dehydrogenase family, member 9, deficiency of^MedGen-Dis | O | 0..1 | **Coding system choices:**   1. **SCT** 2. **MedGen-Dis** 3. **I10C** 4. **I9CDX**   The disorder with which this variant is associated. Allows same coding systems as for disease assessed. MedGen disease carries the part of MedGen’s content that identifies diseases. |
|  |  |  | **Allelic state/phase information** | | | | | |
| B.20 | CNE | [53034-5](http://s.details.loinc.org/LOINC/53034-5.html) | Allelic state | 2.1 | LA6706-1^Heterozygous^LN | C | 0..1 | **Answer List: LL381-5**   |  |  | | --- | --- | | 1. **Heteroplasmic** | **LA6703-8** | | 1. **Homoplasmic** | **LA6704-6** | | 1. **Homozygous** | **LA6705-3** | | 1. **Heterozygous** | **LA6706-1** | | 1. **Hemizygous** | **LA6707-9** |   This variable describes the relationship between the alleles found at the same locus on different chromosomes. It is not always discerned by the study.  Answer list taken from the 2013 HL7 V2 Clinical Genomics Implementation Guide. |
| B.21 | NM | 81258-6 | Allelic Frequency[NFR] | 2.1 | 0.47 | C | 0..1 | Reports the fraction of all of the reads at this genomic location that were represented by the given allele. For homozygotes it will be close to 1.0; for heterozygotes it will be close to 0.5. It can be a smaller number when there are mosaics or multiple chromosome, or mixtures of tumor cells and normal cells. |
| B.22 | NM | 82121-5 | Allelic read depth | 2.1 | 208 | O | 0..1 | Specifies the number of reads that identified the allele in question whether it consists of one or a small sequence of contiguous nucleotides. Different methods and purposes require different numbers of reads to be acceptable. Often >400, sometimes as few as 2-4. |
| B.23 | CWE | 82120-7 | Allelic phase | 2.1 | LA6112-2^1st set of variants in cis relation to each other^LN | O | 0..1 | **Answer List: LL4025-4**   |  |  | | --- | --- | | 1. **1st set of variants in cis relation to each other** | **LA6112-2** | | 1. **2nd set of variants in cis relation to each other** | **LA61 13-0** | | 1. **3rd set of variants in cis relation to each other** | **LA6114-8** | | 1. **4th set of variants in cis relation to each other** | **Answer code pending** | | 1. **5th set of variants in cis relation to each other** | **Answer code pending** | | 1. **Maternal** | **LA26320-4** | | 1. **Paternal** | **LA26321-2** | | 1. **Unknown** | **LA4489-6** | | 1. **Other** | **LA46-8** |   Defines which variations are in cis relationship (on the same chromosome) to one another. The first and second set could be in cis relation to one another and yet not be on the same chromosome. Can accommodate trisomies, mosaics, and other special cases, and distinguish whether the chromosome is maternal or paternal when such details can be inferred (e.g. when the parent’s genotype is also available). |
| B.24 | CWE | 82309-6 | Basis for allelic phase | 2.1 | LA26429-3^Inferred from population data^LN | O | 0..1 | **Answer List: LL4050-2**   |  |  | | --- | --- | | 1. **Directly measured** | **LA26426-9** | | 1. **Family DNA** | **LA26427-7** | | 1. **Family history** | **LA26428-5** | | 1. **Inferred from population data** | **LA26429-3** |   If the allelic phase LOINC 82120-7 (row B.23) is included, this observation should also be included. This identifies the evidential basis on which the allelic phase and/or the allelic state was concluded. |

**If a second and a third simple variant were reported without special meaning together they would show up as additional simple variants with OBX-4 valued with 2.2 for the 2nd set and with 2.3 for the 3rd set of variables.**

### Structural Variants: Report section 3 (Table 4)

Table 4: Report Section 3 for Structural Variations

|  | **OBX-2** | **OBX 3.1** | **OBX 3.2** | **OBX-4** | **OBX-5** | **LOINC Panel/Definitional terms** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Label** | **Type** | **LOINC #** | **LOINC Name** | **Sub ID** | **Example values** | **R** | **Card** | **Term description** |
| C | N/A | **81297-4** | **Genomic structural variant panel** |  | Not included in the message per se. |  | 0..\* | **Repeats for each structural variant.**  Note some structural variants that have well defined break points are carried in ClinVar and can be reported under the simple variant report section using dbVar IDs and/or COSMIC structured variant IDs. |
| C.1 | CWE | 81286-7 | Genomic structural variant [ID] | 3.1 | nsv995237^17p12(chr17:14184616-15581544)x1^dbVar-GL | P | 0..1 | **Coding system choices:**   1. **dbVar-GL** 2. **dbVar-Som**     NCBI separates Germline (dbVar-GL) and Somatic (dbVar-som) dbVar files. So we have separate coding systems (and corresponding look up tables in the LHC Clinical Table Search Service) for each. This variable can accept either somatic or Germline structural variant codes. Message implementers will insert the appropriate coding system in the CWE.3 to indicate the coding system source.  NCBI is the primary focus for this structural variant variable because this is a US specification and because their files carry all of the European (EBI) structural variant as well. Reporters could also code a structural variant with any HL7 OID structural variant identifiers.  The identifiers in the NCBI dbVar table have prefixes of nsv, nssv, esv or essv. Submissions to NCBI begin with n. Submissions to EBI begin with e. There is no overlap between the two sources of submissions. The three letter prefixes identify a set of submissions with the same “location” range and mutation type. The four letter prefixes identify distinct submissions. So a given structured mutation will appear with one nsv (or esv) code and many nssv (or essv) codes. The submission files carry calls and diagnoses and locations, which may vary somewhat across a given nsv (or esv) code. We include both three letter and four letter mutations in our test files. Implementers could constrain to nssv (essv) codes or to nsv (esv) codes as needed.  A structural variant report should include at least one of the following: Genomic structural variant 81286-7 (row C.1), Genomic structural variant name 81290-9 (HGVS expression) or 81291-7 (ISCN) (row C.4). |
| C.2 | CWE | 82119-9 | COSMIC structural variant | 3.1 | Example pending | C | 0..1 | **Coding system:**   1. **COSMIC-Strc**   COSMIC has the kinds of structured variants stored in NCBI’s dbVar, but COSMIC separates them into “structured variants” and “copy number variants” and stores the two kinds in two different tables. We have created a coding system table for what COSMIC stores in its structured variant tables and made it available for look up in the LHC Clinical Table Search Service at: <https://lforms-service.nlm.nih.gov/apidoc/cosmic_struct/v1/doc.html>  This table carries more than 3 million records. And the Identifiers are pure numbers. Users can look up the COSMIC mutation IDs and explore these COSMIC table with our LHC tools with permission. But users may not download any of these files without specific agreement from COSMIC. Copyright Wellcome Trust Sanger Institute (<http://cancer.sanger.ac.uk/cosmic/license>).  We have also defined a *coding system* (and OID) for COSMIC copy number variants (called COSMIC-CPYN), but have not yet created any look up tables because per COSMIC their identifiers are not yet stable. We will add a look up table for COSMIC copy number variants when COSMIC is happy with the identifiers. |
| C.3 | CWE | 81298-2 | Structural variant cytogenetic location | 3.1 | 17p12^17p12^Chrom-Loc | R | 0..\* | **Coding system: Chrom-Loc**  Chromosome location (AKA chromosome locus or cytogenetic location), is the standardized syntax for recording the position of genes and large mutations. It consists of three parts: the Chromosome number (e.g. 1-22, X, Y), an indicator of which arm – either “p” for the short or “q” for the long, and then a series of numbers separated by dots that indicate the band, sub band and sub-sub band of the locus (e.g. 2p16.3). There are other conventions for reporting ranges and locations at the ends of the chromosomes.  The table of these chromosome locations was loaded with all of the locations found in NCBI’s ClinVar variation tables. It will expand as additional sources become available. This may not include all finely grained chromosome locations that exist. Users can add to it as needed. We have not found a table of chromosome locations with standard codes. **Balloters: if you know of a publicly available and maintained list of chromosome locations with standard codes please forward to us.** |
| C.4 | CWE | 81290-9 | Structural variant HGVS expression | 3.1 | NC\_000017.11:g.(?\_14184616)\_(15581544\_?)dup^ NC\_000017.11:g.(?\_14184616)\_(15581544\_?)dup ^HGVS.g | C | 0..1 | **Coding system: HGVS.g**  One of the Row C.3 Structural variant HGVS (#81290-9) or Row C.4 (structural variant ISCN) should be included with every structural variant report. **Balloters**: **The type of structural variant is commonly reported as part of the HGVS expression by both NCBI and COSMIC but we don’t know if the type is a required part of the HGVS expression –Please comment.**  Taken from PMID: [21309030](http://www.ncbi.nlm.nih.gov/pubmed/21309030) |
| C.5 | CWE | 81291-7 | Structural variant ISCN | 3.1 | Example pending | C | 0..1 | **Coding System: ISCN**  Like HGVS, ISCN is a syntax. It came out of cytopathology and its focus ranges from normal and abnormal chromosome numbers (e.g. XXX down to smallish copy number changes).  The full syntax is described in : ISCN (2016): An International System for Human Cytogenetic Nomenclature, J McGowan-Jordan, A. Simons, M. Schmid (eds). S. Karger, Basel 2013. ISBN: 978-3-318-05857-4 |
| C.6 | NM | 82155-3 | Genomic structural variant copy number | 3.1 | 1 | **O** | 0..1 | The copy number of the large variant when applicable. In HGVS, this is the numeric value following the “X”. It is a unit-less value. Note that a copy number of 1 implies a deletion. The copy number can usually be inferred from the HGVS or ISCN fields. |
| C.7 | NR | 81287-5 | Genomic structural variant start-end | 3.1 | 14184616^15581544 | O | 0..1 | The reported start and end of the structural variant, when distinctions between outer bound and inner bounds are not made. A common reality. (See Rows G and Row H). |
| C.8 | NM | 81299-0 | Genomic structural variant reported arrCGH ratio | 3.1 | .48 | C | 0..1 | Usually only applicable to ArrCGH and related studies.  Its value is a number less than 1. |
| C.9 | CWE | 81289-1 | DNA structural variation type | 3.1 | LA6686-5^Deletion^LN | O | 0..1 | **Answer List: LL4033-8**   |  |  | | --- | --- | | 1. **Copy number gain** | **LA14033-7** | | 1. **Copy number loss** | **LA14034-5** | | 1. **Duplication** | **LA6686-5** | | 1. **Deletion** | **LA6692-3** | | 1. **Insertion** | **LA6687-3** | | 1. **Mobile element insertion** | **LA26324-6** | | 1. **Novel sequence insertion** | **LA26325-3** | | 1. **Tandem duplication** | **LA26326-1** | | 1. **Inversion** | **LA6689-9** | | 1. **Intrachromosomal breakpoint** | **LA26327-9** | | 1. **Interchromosomal breakpoint** | **LA26328-7** | | 1. **Translocation** | **LA26331-1** | | 1. **Complex** | **LA26330-3** | | 1. **Sequence alteration** 2. **Insertion/Deletion** | **LA26329-5**  **LA9659-9** |   Answer list is taken from the NCBI dbVar website  <http://www.ncbi.nlm.nih.gov/dbvar/content/overview/>  which was taken from Sequence Ontology <http://www.sequenceontology.org/resources/>.  The DNA structural variation type is also often carried in the HGVS expression, but as a shortened abbreviation. |
| C.10 | NM | 81300-6 | Structural variant length | 3.1 | 1396929 | O | 0..1 | This content is uncommon in today’s clinical reports. (The units of measure are base pairs.) |
| C.11 | NR | 81301-4 | Structural variant outer start and end | 3.1 | 13200589^15592000 | O | 0..1 | This content taken with inner start-end provides a way to describe the uncertainty in the edge positions of structured variation. These are attributes in the NCBI submission file for dbVar, but are not commonly reported today. |
| C.12 | NR | 81302-2 | Structural variant inner start and end | 3.1 | 14184616^15581544 | O | 0..1 | This content is uncommon in today’s clinical reports. (See Row C1.12) |
| C.13 | CWE | 81304-8 | Structural variant method type | 3.1 | LA26398-0^Sequencing^LN | P | 0..1 | **Answer List: LL4048-6**   |  |  | | --- | --- | | 1. **Sequencing** | **LA26398-0** | | 1. **Oligo aCGH** | **LA26399-8** | | 1. **SNP Array** | **LA26400-4** | | 1. **BAC aCGH** | **LA26401-2** | | 1. **Curated** | **LA26402-0** | | 1. **Digital Array** | **LA26403-8** | | 1. **FISH** | **LA26404-6** | | 1. **Gene Expression Array** | **LA26405-3** | | 1. **Karyotyping** | **LA26406-1** | | 1. **MAPH** | **LA26407-9** | | 1. **MassSpec** | **LA26408-7** | | 1. **Merging** | **Answer code pending** | | 1. **Multiple Complete Digestion** | **LA26414-5** | | 1. **MLPA** | **LA26415-2** | | 1. **Optical Mapping** | **LA26417-8** | | 1. **PCR** | **LA26418-6** | | 1. **qPCR (Real-time PCR)** | **LA26419-4** | | 1. **ROMA** | **LA26420-2** |   Taken from NCBI's dbVAR data submission template.  2015 review of the newest methods at: PMCID: PMC4479793  The specification for structural variants includes a type of method section because the precision of the start and end position of this kind of variation is determined so strongly by the type of method. |

### Pharmacogenomics: Report section 4 (Table 5)

Table 5: Report Section 4 for Reporting Pharmacogenomics Studies (The detailed allelic Content could be reported in Section 5 and Linked to the results)

|  | **OBX-2** | **OBX 3.1** | **OBX 3.2** | **OBX-4** | **OBX-5** | **LOINC Panel/Definitional terms** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Label** | **Type** | **LOINC #** | **LOINC name** | **Sub ID** | **Example values** | **R** | **Card** | **Term description** | | |
| D1 | D | 82118-1 | **Pharmacogenomics results panel** |  |  |  | 0.\* | Will repeat for each gene tested | | |
|  |  |  | **Results for first gene in the study** | | | | | |
| D1.1 | CNE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene(s) studied | 4.1 | 2623^CYP2C9^HGNC-Symb~  23663^VKORC1^HGNC-Symb |  | 1..3 | **Coding system: HGNC-Symb**  Identifies the genes known to influence drug metabolism or efficacy being tested for relevant mutations.  In some cases, such as in the example of CYP2C9 and VKORC1, changes in more than one gene are required to cause the reported effect on a specific drug’s metabolism or efficacy, in which case the genes with the combined effect should be listed in one OBX-5 separated by the repeat delimiter. | | |
| D1.2 | ST | 47998-0 | Genotype display name  Display name (general) | 4.1 | \*2/\*5~\*A/\*A |  | 1..3 | In this context, the corresponding alleles for each of the genes listed under gene(s) studied are also shown separated by a slash e.g., \*1/\*2 as is the common format.  If the metabolism/efficacy effect is based on 2 genes, the results for each gene are shown separated by the repeat delimiter in the same order as the gene symbols are displayed in gene(s) studied observation. E.g. \*2/\*5~\*A/\*A. Then the interpretation variables e.g., 53040-2, the effect on metabolism or 51961-1 the effect on efficacy specify the combined effect of the multiple alleles recorded in this variable.  This content, the previous and the next depend strongly on the use of within OBX-5 repeats. So these whole OBX’s should not repeat. | | |
| D1.3 | TX | New LOINC | Cross reference to genetic details | 4.1 | 5.1~5.2 |  | 0..\* | **Store the OBX-4 value.**  In the example there are four alleles, \*2 , \*5, \*A and \*A. If the reporter wanted to link each star allele to the full genetic details reported in other report sections, he/she would store the linkage in this LOINC code (to be provided) here.  The OBX reporting the linkage would repeat for each allele about which the full genetic details were being reported. In this example above, we have two genes with four alleles. So would require four linkage pointer OBX-X’s. The first OBX would apply to the first allele, \*2, the second to \*5, the third to \*A, the fourth, which might be redundant would also apply to \*A. (In most cases only two alleles would be present). The value(s) recorded in the cross reference would be the OBX-4 value of the panel(s) in other parts of the report where the detailed genetic results were recorded. As we have defined the values for OBX-4 all of the OBX’s in one panel will have the same OBX-4 and it will apply to that panel and only that panel in the repeat.  To link an allele to one simple variant- one would store that OBX-4 value for the simple variant panel of interest into the linkage field. For example, if the linkage was to the first of a simple variant panel you would record 2.1 (2 to indicate it was a simple panel and 1 to indicate that it was the first of such panels. If the allele was defined on the basis of many simple variants , say the 1st, 3rd and 4th,  then you identify them via a list -- 2.1~2.3~2.4 -- in the linkage OBX.  Analogues rules could be used to link to structural variants, except that the linkage Ox’s would begin with 3, e.g. 3.1 to identify the first structural variant. The same would apply to linkage to a complex variant where the OBX value would begin with 5, say 5.1 or 5.3. Different types of references could be mixed in the same linkage OBX. Say 2.2~2.4~3.2 if the linkage was to the second and third simple variant and the second structural variant. The same could apply to complex variants, but in most cases the one complex variant will be enough to specify what is needed.  **Balloters please comment on this proposed approach to linkage.** | | |
| D1.4 | CNE | 53040-2 | Genetic variation’s effect on drug metabolism interp | 4.1 | LA9657-3^Rapid metabolizer^LN | C | 0..1 | **Answer List:** [**LL3856-3**](http://r.details.loinc.org/AnswerList/LL3856-3.html)   |  |  | | --- | --- | | 1. **Ultrarapid metabolizer** | **LA10315-2** | | 1. **Rapid metabolizer** | **LA25390-8** | | 1. **Normal metabolizer** | **LA25391-6** | | 1. **Intermediate metabolizer** | **LA10317-8** | | 1. **Poor metabolizer** | **LA9657-3** |   For pharmacogenomics studies, one of 53040-2 (effect on drug metabolism) and/or 51961-1 (effect on drug efficacy) must be included in the panel. Answer list comes from CPIC, a professional society (<https://cpicpgx.org/wp-content/uploads/2016/01/CPIC_term_standardization_project_final_terms.pdf>). See also [PMID: 27441996](http://www.ncbi.nlm.nih.gov/pubmed/27441996) which also includes a discussion about how to describe transporter function, but how to include those specifics has not been decided. | | |
| D1.5 | CWE | 51961-1 | Genetic variation’s effect on drug efficacy interp | 4.1 | NA | C | 0..1 | **Answer List: LL539-8**   |  |  | | --- | --- | | 1. **Resistant** | **LA6676-6** | | 1. **Responsive** | **LA6677-4** | | 1. **Presumed resistant** | **LA9660-7** | | 1. **Presumed responsive** | **LA9661-5** | | 1. **Unknown significance** | **LA6682-4** | | 1. **Benign** | **LA6675-8** | | 1. **Presumed Benign** | **LA6674-1** | | 1. **Presumed non-responsive** | **LA9662-3** |   For pharmacogenomics studies, 53040-2 (effect on drug metabolism) and/or 51961-1 (effect on drug efficacy) must be included in the panel. Answer list comes from the 2013 HL7 V2 Clinical Genomics Implementation Guide. | | |
| E1 | - | 82117-3 | Medication usage implications panel |  | This term identifies the set of LOINC terms that are part of the panel but not part of the message | O | 0..\* | 1st medication assessed under the first gene or pair of genes studies.  Provides a way to present the guidance about specific drugs or drug classes. May repeat for as many drugs as relevant to the tested gene(s).  This, or more extensive, information can also be included as part of the results for the overall report PDF as it is commonly done now (See LOINC 51969-4 Full narrative report in row A.11 provided for that purpose). | | |
| E1.1 | CWE | 51963-7 | Medication assessed | 4.1.1 | 11289^Warfarin^RxT-Ingrd | R | 1..1 | **Coding system: RxT-Ingrd**  This variable identifies the medication about which assessments will be made in the next two fields  Required if medication usage panel is employed.  If there are cases where the guidance for many different drugs could be the same, we could consider proposing within OBX-5 repeats. | | |
| E1.2 | CWE | 82116-5 | Medication usage suggestion [type] | 4.1.1 | LA26423-6^Increase dose^LN | C | 0..1 | **Answer List: LL4049-4**   |  |  | | --- | --- | | 1. **Consider Alternative Medication** | **LA26421-0** | | 1. **Decrease Dose** | **LA26422-8** | | 1. **Increase Dose** | **LA26423-6** | | 1. **Use Caution** | **LA26424-4** | | 1. **Normal Response Expected** | **LA26425-1** |   This variable (82116-5) or the following -- at least one of the medication usage type or narrative -- should be included when any drug is named in Row E1.1.  There is little consistency in the answer lists for this variable as used by different laboratories. We could not find an authoritative source, so the above list was our best approximation**. So balloters, if you know of a better and authoritative answer list please suggest it and give us the source.** | | |
| E1.3 | TX | New LOINC | Medication usage suggestion [narrative] | 4.1.1 | May need higher dosage than usual. | C | 0..1 | Used to deliver whatever specific content, in narrative, laboratories want to deliver. At least one of the medication usage type or narrative variables should be included when the panel is implemented. | | |
| D2 | D | 82118-1 | **Pharmacogenomics results panel** |  |  |  | 0.\* | Will repeat for each gene tested | | |
|  |  |  | **Results for second gene in study** | | | | | |
| D2.1 | CNE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene studied | 4.2 | 2623^CYP2C9^HGNC-Symb |  | 1..3 | See description in previous instance of same term LOINC # 48018-6 in row D1.1. | | |
| D2.2 | ST | 47998-0 | Genotype display name | 4.2 | \*2/\*5 |  | 1..3 | See description in previous instance of same term LOINC# 47998-0 in row D1.2. | | |
| D2.3 | ST | New LOINC | Cross reference to full genetic details | 4.2 | Example pending |  |  | See description in previous instance of same term LOINC# \_\_\_ in row D1.3. | | |
| D2.4 | CWE | 53040-2 | Genetic variation’s effect on drug metabolism interp | 4.2 | LA9657-3^Poor metabolizer^LN | C | 0..1 | See description in previous instance of same term LOINC# 53040-2 in row D1.4. | | |
| D2.5 | CWE | 51961-1 | Genetic variation’s effect on drug efficacy interp | 4.2 | NA | C | 0..1 | See description in previous instance of same term LOINC# 51961-1 in row D1.5. | | |
| E2 | N/A | 82117-3 | Medication usage implications panel |  |  | O | 0..\* | See description in previous instance of same term LOINC# 82117-3 in row E1. | | |
| E2.1 | CWE | 51963-7 | Medication assessed | 4.2.1 | 611247^Fluoxetine^RxT-ingd | R | 1..1 | See description in previous instance of same term, LOINC # 51963-7, in row E1.1. | | |
| E2.2 | \*CWE | 82116-5 | Medication usage suggestion [type] | 4.2.1 | LA26421-0^Consider Alternative Dose^LN | C | 0..1 | See description in previous instance of same term LOINC# 82116-5 in row E1.2. | | |
| E2.3 | TX | New LOINC | Medication usage suggestion [narrative] | 4.2.1. | Monitor for inhibition of other drugs. | C | 0..1 | See description in previous instance of same term LOINC# 82116-5 in row E1.3 | | |
| E2a | N/A | 82117-3 | Medication usage implications panel |  |  | O | 0..\* | See description in previous instance of same term LOINC# 82117-3 in row E1. | | |
| E2.1a | CWE | 51963-7 | Medication assessed | 4.2.2 | 7258^Naproxen^RxT-ingd | R | 1..1 | See description in previous instance of same term, LOINC # 51963-7, in row E1.1. | | |
| E2.2a | \*CWE | 82116-5 | Medication usage suggestion [type] | 4.2.2 | LA264214-4^Use Caution^LN | C | 0..1 | See description in previous instance of same term LOINC# 82116-5 in row E1.2. | | |
| E2.3a | TX | New LOINC | Medication usage suggestion [narrative] | 4.2.2 | Monitor for inhibition of other drugs. | C | 0..1 | See description in previous instance of same term LOINC# 82116-5 in row E1.3 | | |
| D3 | D | 82118-1 | **Pharmacogenomics results panel** |  |  |  | 0.\* | Will repeat for each gene tested | | |
|  |  |  | **Results for third gene or gene pair studied** | | | | | |
| D3.1 | CNE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene(s) studied | 4.3 | 2621^CYP2C19^HGNC-Symb |  | 1..3 | See description in previous instance of same term LOINC # 48018-6 in row D1.1. | | |
| D3.2 | ST | 47998-0 | Genotype display name | 4.3 | \*1/\*1 |  | 1..3 | See description in previous instance of same term LOINC# 47998-0 in row D1.2. | | |
| D3.3 | ST | New LOINC | Cross reference to full genetic details | 4.3 | Example pending |  |  | See description in previous instance of same term LOINC# (code pending) in row D1.3. | | |
| D3.4 | CWE | 53040-2 | Genetic variation’s effect on drug metabolism interp | 4.3 | LA25391-6^Normal metabolizer^LN | C | 0..1 | See description in previous instance of same term LOINC# 53040-2 in row D1.4. | | |
| D3.5 | CWE | 51961-1 | Genetic Variation’s effect on drug efficacy interp | 4.3 | NA | C | 0..1 | See description in previous instance of same term LOINC# 51961-1 in row D1.5. | | |
| E3 | N/A | 82117-3 | Medication usage implications panel |  |  | O | 0..\* | See description in previous instance of same term LOINC# 82117-3 in row E1. | | |
| E3.1 | CWE | 51963-7 | Medication assessed | 4.3.1 | 6754^Meperidine^RxT-ingd | R | 1..1 | See description in previous instance of same term, LOINC # 51963-7, in row E1.1. | | |
| E3.2 | \*CWE | 82116-5 | Medication usage suggestion [type] | 4.3.1 | LA26425-1^Usual dosage^LN | C | 0..1 | See description in previous instance of same term LOINC# 82116-5 in row E1.2. | | |
| E3.3 | TX | New LOINC | Medication usage suggestion [narrative] | 4.3.1 | In usual dosages | C | 0..1 | See description in previous instance of same term LOINC# 82116-5 in row E1.3 | | |
| D4 | D | 82118-1 | **Pharmacogenomics results panel** |  |  |  | 0.\* | Will repeat for each gene tested | |
|  |  |  | **Results for fourth gene or gene pair studied** | | | | | | |
| D4.1 | CNE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene(s) studied | 4.4 | 2637^CYP3A4^HGNC-Symb ~2638^CYP3A5^HGNC-Symb |  | 1..3 | See description in previous instance of same term LOINC # 48018-6 in row D1.1. | |
| D4.2 | ST | 47998-0 | Genotype display name | 4.4 | \*1/\*1~\*1/\*1 |  | 1..3 | See description in previous instance of same term LOINC# 47998-0 in row D1.2. | |
| D4.3 | ST | New LOINC | Cross reference to full genetic details | 4.4 | NA |  |  | See description in previous instance of same term LOINC# \_\_\_ in row D1.3. | |
| D4.4 | CWE | 53040-2 | Genetic variation’s effect on drug metabolism interp | 4.4 | LA25391-6^Rapid Metabolizer^LN | C | 0..1 | See description in previous instance of same term LOINC# 53040-2 in row D1.4. | |
| D4.5 | CWE | 51961-1 | Genetic Variation’s effect on drug efficacy interp | 4.4 | Not applicable to this example | C | 0..1 | See description in previous instance of same term LOINC# 51961-1 in row D1.5. | |

### Complex Variants: report section 5 (Table 6)

Table 6: Report Section 5 for Reporting Complex Variants (those with multiple alleles)

*NOTE: We have moved complex variants to the last section because it is a very long example, they are most applicable to pharmacogenomics and such reports do not always go into the details of the simple variants within the haplotypes.*

| **Label** | **OBX-2** | **OBX 3.1** | **OBX 3.2** | **OBX-4** | **OBX-5** | **LOINC Panel/Definitional terms** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Type | LOINC # | LOINC Name | Sub ID | Example values | R | Card | Term description |
| F |  | **81251-1** | **Complex genetic variant – panel** |  |  |  |  | **(repeats for each complex variant)**  Complex variants are made up of two or more simple variants which together have phenotypic implications. Usually they carry information about phase (i.e. whether reported chromosomes are on same or different chromosome). Would be needed for detailed haplotype and compound hets among other types.  In the OBX’s that follow OBX-4 increments by 1 for each repeated complex variant. The example only presents one Complex variant |
|  |  |  | **Information that applies to one complex variant as a whole** | | | | | |
| F.1 | CWE | 81260-2 | Complex genetic variant | 5.1 | 16895^NM\_000106.5(CYP2D6):c.[886C>T;457G>C] – Haplotype^CLINVAR-V | C | 0..1 | **Coding System: CLINVAR-V**  Following the pattern of simple variant, the code is the identifier from a public genetic database and the name is a concatenation of the RefSeq, the gene symbol, the HGVS describing the multiple variants, and the complex variant type. |
| F.2 | CWE | 81262-8 | Complex variant HGVS name | 5.1 | c.[886C>T;457G>C]^ c.[886C>T;457G>C]^HGVS.c | C | 0..1 | **Coding System: HGVS.c**  Includes HGVS for the separate variants that make this complex variant. The square bracket surrounding multiple variants indicates they are together on one chromosome. When each simple variant is surrounded by square brackets that means they are on separate chromosomes. HGVS syntax can also assert that the phase is unknown. |
| F.3 | CWE | 81263-6 (changed from 81265-6) | Complex variant type | 5.1 | LA26218-0^Haplotype^LN | O | 0..1 | **Answer List: LL3991-1**   |  |  | | --- | --- | | 1. **Compound heterozygous** | **LA26217-2** | | 1. **Double heterozygous** | **LA26220-6** | | 1. **Haplotype** | **LA26218-0** | | 1. **Hemizygous (will need to edit)** | **LA6707-9** | |
| F.4 | CWE | 81259-4 | Associated phenotype | 5.1 | 688395015^Debrisoquine adverse reaction (disorder)^SCT | O | 0..1 | **Coding system choices:**   1. **SCT** 2. **MedGen-Dis** 3. **I10C** 4. **I9CDX**   Disorder with which this complex variant is associated. |
| F.5 | CNE | [53037-8](http://s.details.loinc.org/LOINC/53037-8.html) | Genetic variation clinical significance [Imp] | 5.1 | LA6668-3^Pathogenic^LN | O | 0..1 | **See the LOINC# 53058-9 in row B.17. for answer lists**  This is the significance of the many simple variants in the first complex variant taken together. |
| F.6 | CNE | [53034-5](http://s.details.loinc.org/LOINC/53034-5.html) | Allelic state | 5.1 | LA6706-1^Heterozygous^LN | O | 0..1 | **See same term in simple variant- LOINC # 53034-5 in row B.20.** But this is the allelic state of the many simple variants taken together in the complex variant. (It will not apply to all complex variant types). |
| F.7 | CWE | 82309-6 | Basis for allelic phase | 5.1 | LA26429-3^Inferred from population data | O | 0..1 | Refer to term that defines it in Row B.24 |
|  |  |  | **Information that applies to the simple variant(s) that make up the complex variant (one at a time)** | | | | | |
| B1 |  | **81250-3** | **Simple genetic variant panel** | N/A | This LOINC code will not be included in the message if we use the OBX-4 instead of nested OBR’s to organize the hierarchy. |  | 1..\* | **1st simple variant within the first complex variant. Same as stand-alone simple variant panel** |
| B1.1 | CWE | 81252-9 | Simple genetic variant | 5.1.1 | 31934^NM\_000106.5(CYP2D6):c.886C>T (p.Arg296Cys)^CLINVAR-V | C | 0..1 | See description in previous instance of same term LOINC# 81252-9 in row B.1. |
|  |  |  | **Transcript specification** | | | | | |
| B1.2 | CWE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene studied [ID] | 5.1.1 | 2625^CYP2D6^HGNC-Symb | C | 0..1 | See description in previous instance of same term LOINC# 48018-6 in row B.2. |
| B1.3 | CWE | 51958-7 | Transcript Reference Sequence ID | 5.1.1 | NM\_000106.5^ NM\_000106.5^RefSeq-T | C | 0..1 | See description in previous instance of same term LOINC# 51958-7 in row B.3. |
| B1.4 | CWE | [48004-6](http://s.details.loinc.org/LOINC/41103-3.html) | DNA change HGVS.c | 5.1.1 | c.886C>T^ c.886C>T ^HGVS.c | C | 0..1 | See description in previous instance of same term LOINC # 48004-6 in row B.4. |
| B1.5 | CWE | [48005-3](http://s.details.loinc.org/LOINC/48005-3.html) | Amino acid change pHGVS: | 5.1.1 | p.Arg296Cys^ p.Arg296Cys ^HGVS.p | C | 0..1 | See description in previous instance of same term LOINC# 48005-3 in row B.5. |
| B1.6 | CWE | 48019-4 | DNA change [type] | 5.1.1 | LA6690-7^Substitution^LN | O | 0..1 | See description in previous instance of same term LOINC# 48019-4 in row B.6. |
| B1.7 | CWE | 48006-1 | Amino acid change [type] | 5.1.1 | LA6698- 0^Missense^LN | O | 0..1 | See description in previous instance of same term LOINC# 48006-1 in row B.7. |
|  |  |  | **Genomic specification – a VCF-like organization** | | | | | |
| B1.8 | CWE | 48013-7 | Genomic Reference Sequence [ID] | 5.1.1 | NG\_008376.3^ NG\_008376.3^RefSeq-G | C | 0..1 | See description in previous instance of same term LOINC# 48013-7 in row B.8. |
| B1.9 | ST | [69547-8](http://s.details.loinc.org/LOINC/69547-8.html) | Genomic Ref allele | 5.1.1 | C | C | 0..1 | See description in previous instance of same term LOINC# 69547-8 in row B.9. |
| B1.10 | NM | 81254-5 | Genomic Allele start-end | 5.1.1 | 42127941 | C | 0..1 | See description in previous instance of same term LOINC# 81254-5 in row B.10. |
| B1.11 | ST | [69551-0](http://s.details.loinc.org/LOINC/69551-0.html) | Genomic Alt allele | 5.1.1 | T | C | 0..1 | See description in previous instance of same term LOINC# 69551-0 in row B.11. |
|  |  |  | **Other optional codes related to simple variation** | | | | | |
| B1.12 | CWE | 48004-6 | dbSNP ID | 5.1.1 | rs16947^rs16947^dbSNP | O | 0..1 | See description in previous instance of same term LOINC# 48004-6 in row B.12. |
| B1.13 | CWE | 81256-0 | COSMIC | 5.1.1 | NA | C | 0..1 | See description in previous instance of same term LOINC# 81256-0 in row B.13. |
| B1.14 | CWE | 81257-8 | CIGAR | 5.1.1 | NA | O | 0..1 | See description in previous instance of same term LOINC# 81257-8 in row B.14. |
|  |  |  | **Other possible attributes** | | | | | |
| B1.15 | CWE | 48001-2 | Chromosome location of genetic variant | 5.1.1 | 22q13.2^22q13.2^Chrom-Loc | O | 0..\* | See description in previous instance of same term LOINC# 48001-2 in row B.15. |
| B1.16 | CWE | 48002-0 | Genomic source class [Type] | 5.1.1 | LA6683-2^Germline^LN | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.16. |
|  |  |  | **Interpretations** | | | | | |
| B1.17 | CNE | [53037-8](http://s.details.loinc.org/LOINC/53037-8.html) | Genetic variation clinical significance[Imp] | 5.1.1 | NA | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.17. |
| B1.18 | CWE | 69548-6 | Genetic variant assessment [Imp] | 5.1.1 | LA9633-4^Present^LN | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.18. |
| B1.19 |  | 81259-4 | Probable associated phenotype [Imp] | 5.1.1 | NA | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.19. |
|  |  |  | **Allelic state / phase information** | | | | | |
| B1.20 | CNE | [53034-5](http://s.details.loinc.org/LOINC/53034-5.html) | Allelic state | 5.1.1 | LA6706-1^Heterozygous^LN | C | 0..1 | See description in previous instance of same term - LOINC # 53034-5 in row B.20. |
| B1.21 | NM | 81258-6 | Allelic Frequency[NFR] | 5.1.1 | 0.47 | O | 0..1 | See description in previous instance of same term LOINC# 81258-6 in row B.21. |
| B1.22 | NM | 82121-5 | Allelic read depth | 5.1.1 | 208 | O | 0..1 | See description in previous instance of same term – LOINC# 53058-9 in row. B.22. |
| B1.23 | CWE | 82120-7 | Allelic phase | 5.1.1 | LA6112-2^1st set of variants in cis relation to each other^LN | O | 0..1 | See description in previous instance of same term -- LOINC# 81259-4 in row B.23. |
| B1.24 | CWE | 82309-6 | Basis for allelic phase |  | LA26429-3^Inferred from population data^LN | O | 0..1 | See description in previous instance of same term -- LOINC# 81259-4 in row B.24. |
| **B2** |  | **81250-3** | **Simple genetic variant panel** |  |  |  |  | **2nd Simple variant within complex variant. Same as stand-alone simple variant panel --** |
| B2.1 | CWE | 48008-7 | Simple genetic variant | 5.1.2 | 38485^NM\_000106.5(CYP2D6):c.1457G>C (p.Ser486Thr)^CLINVAR-V |  | 0..1 | See description in previous instance of same term LOINC# 81252-9 in row B.1. |
|  |  |  | **Transcript specification** | | | | | |
| B2.2 | CWE | [48018-6](http://s.details.loinc.org/LOINC/48018-6.html) | Gene studied [ID] | 5.1.2 | 2625^CYP2D6^HGNC-Symb | C | 0..1 | See description in previous instance of same term LOINC# 48018-6 in row B.2. |
| B2.3 | CWE | 51958-7 | Transcript Reference Sequence ID | 5.1.2 | NM\_000106.5^ NM\_000106.5^RefSeq-T | C | 0..1 | See description in previous instance of same term LOINC# 51958-7 in row B.3. |
| B2.4 | CWE | [41103-3](http://s.details.loinc.org/LOINC/41103-3.html) | DNA change HGVS.c: | 5.1.2 | c.1457G>C^ c.1457G>C ^HGVS.c | C | 0..1 | See description in previous instance of same term LOINC # 48004-6 in row B.4. |
| B2.5 | CWE | [48005-3](http://s.details.loinc.org/LOINC/48005-3.html) | Amino acid change pHGVS | 5.1.2 | p.Ser486Thr^ p.Ser486Thr ^HGVS.p | C | 0..1 | See description in previous instance of same term LOINC# 48005-3 in row B.5. |
| B2.6 | CWE | 48019-4 | DNA change [type] | 5.1.2 | LA6690-7^Substitution^LN | C | 0..1 | See description in previous instance of same term LOINC# 48019-4 in row B.6. |
| B2.7 | CWE | 48006-1 | Amino acid change [type] | 5.1.2 | LA6698-0^Missense^LN | O | 0..1 | See description in previous instance of same term LOINC# 48006-1 in row B.7. |
|  |  |  | **Genomic specification - a VCF-like organization** | | | | | |
| B2.8 | CWE | 48013-7 | Genomic Reference Sequence [ID] | 5.1.2 | NG\_008376.3^ NG\_008376.3^RefSeq-G | C | 0..1 | See description in previous instance of same term LOINC# 48013-7 in row B.8. |
| B2.9 | ST | [69547-8](http://s.details.loinc.org/LOINC/69547-8.html) | Genomic Ref allele | 5.1.2 | G | C | 0..1 | See description in previous instance of same term LOINC# 69547-8 in row B.9. |
| B2.10 | NM | 81254-5 | Genomic Allele start-end | 5.1.2 | 42126611 | C | 0..1 | See description in previous instance of same term LOINC# 81254-5 in row B.10. |
| B2.11 | ST | [69551-0](http://s.details.loinc.org/LOINC/69551-0.html) | Genomic Alt allele | 5.1.2 | C | C | 0..1 | See description in previous instance of same term LOINC# 69551-0 in row B.11. |
|  |  |  | **Other optional codes related to simple variation** | | | | | |
| B2.12 | CWE | 48004-6 | dbSNP | 5.1.2 | rs[368949613](http://www.ncbi.nlm.nih.gov/snp/368949613)^ rs[368949613](http://www.ncbi.nlm.nih.gov/snp/368949613)^dbSNP | O | 0..1 | See description in previous instance of same term LOINC# 48004-6 in row B.12. |
| B2.13 | CWE | 81256-0 | COSMIC | 5.1.2 | NA | C | 0..1 | See description in previous instance of same term LOINC# 81256-0 in row B.13. |
| B2.14 | CWE | 81257-8 | CIGAR | 5.1.2 | NA | O | 0..1 | See description in previous instance of same term LOINC# 81257-8 in row B.14. |
|  |  |  | **Other possible attributes** | | | | | |
| B2.15 | CWE | 48001-2 | location of genetic variant | 5.1.2 | 22q13.2 | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.15. |
| B2.16 | CWE | 48002-0 | Genomic source class [Type] | 5.1.2 | LA6683-2^Germline^LN | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.16. |
|  |  |  | **Interpretations** | | | | | |
| B2.17 | CNE | [53037-8](http://s.details.loinc.org/LOINC/53037-8.html) | Genetic variation clinical significance[Imp] | 5.1.2 | NA | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.17. |
| B2.18 | CWE | 69548-6 | Genetic variant assessment [Imp] | 5.1.2 | LA9633-4^Present^LN | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.18. |
| B2.19 |  | 81259-4 | Probable associated phenotype [Imp] | 5.1.2 | NA | O | 0..1 | See description in previous instance of same term LOINC# 48001-2 in row B.19. |
|  |  |  | **Allelic state and interpretive attributes** | | | | | |
| B2.20 | CNE | [53034-5](http://s.details.loinc.org/LOINC/53034-5.html) | Allelic state | 5.1.2 | LA6706-1^Heterozygous^LN | C | 0..1 | See description in previous instance of same term - LOINC # 53034-5 in row B.20. |
| B2.21 | NM | 81258-6 | Allelic Frequency[NFR] | 5.1.2 | 0.47 | P | 0..1 | See description in previous instance of same term LOINC# 81258-6 in row B.21. |
| B2.22 | NM | 82121-5 | Allelic read depth | 2.1 | 208 | O |  | See description in previous instance of same term – LOINC# 53058-9 in row B.22. |
| B2.23 | CWE | 82120-7 | Allelic phase | 2.1 | LA6112-2^1st set of variants in cis relation to each other^LN | O |  | See description in previous instance of same term -- LOINC# 81259-4 in row B.23. |
| B2.24 | CWE | 82309-6 | Basis for allelic phase |  | LA26429-3^Inferred from population data^LN | O |  | See description in previous instance of same term -- LOINC# 81259-4 in row B.24. |

**If there were a second complex variant in the report it would identified with 5.2 and its first constituent simple variants as 5.2.1 and variables in the second a 5.2.2 etc.**

## Comments on the number of LOINC codes and panels in this genetics message structure

Depending on the kind of analysis, clinical genomic reports will usually include observations from only two or three sections. Almost all reports will carry some variables from section 1, which carries attributes that apply to the whole report. Typical mutation analysis will carry content from Section 2, and/or Section 3. Pharmacogenomics reports that we have seen will typically carry only variables from section 1 and section 4, but some pharmacogenomics labs want to be able to send the detailed genetic data that underlies their star allele results, and that could require content from any of the sections. (See OBX-4 based linking mechanism proposed below.)

We have included many variables (think of the LOINC codes as the equivalent of fields) to satisfy the interest of many kinds of reporting services and receivers. Section 5.4.1 carries 24 different variables! But most of these are optional and some represent alternative ways of saying the same thing. For example the ClinVar coding system ID is informationally equivalent to more than 10 of the variables that follow, because they are carried in the ClinVar record that is identified 999999 in Row B.1. Indeed the LHC demo form auto-populates these variable when you identify a specific ClinVar record. We include these 10 components as separate observations so that reporters can fill this information in themselves when they are reporting a variation that is not registered, and to make it easier for receivers to access these individual components. Thus, the very large number of variables in the simple mutation panel should not be off-putting. Much of what is currently reported could be reported by filling in one variable: LOINC #81252-9 (row B1) using the coding system from ClinVar or COSMIC simple mutation codes. Further, the name of that variable includes the reference sequence, the gene symbol, the c.HGVS and the p.HGVS in one variable. We have not included a variable for HGVS expressions at the genomic level, which would allow an equally compact way to report genomic level variants. **Balloters – should we include such a variable for symmetry’s sake?**

The bottom line is that a given laboratory will not have to use many of these LOINC codes to enrich their narrative report with a few important structured elements. So those interested in minimalist reports could report simple variants with one or two LOINC codes. However, we strongly encourage the inclusion of selected variables from among those defined here (along with your traditional narrative report) for the purposes of decision support and clinical research.

## Availability of the LOINC codes, the hierarchical relationships and the short answers lists in a downloadable electronic format

Don’t worry about parsing out the content of Table 2 through Table 6 to build messages. LOINC provides a mechanism for downloading any panel as an Excel spreadsheet with three worksheets. The one you will want is LOINC# 81247-9 Master genetic variation reporting panel**. (Balloters --should we add “HL7 V2” to the name of this term?)** The first worksheet, called “FORMS” carries the hierarchy in a table of parent-child relationships with the parent (panel) LOINC code in one column and the child LOINC codes in another column. The second worksheet, called “LOINCS” carries the LOINC terms used in the panel and a host of attributes per LOINC term. The third worksheet called “ANSWERS” carries all of the short answer lists, with their codes, names, and other attributes. The download does not yet carry the coding system names tied to their respective LOINC codes.

This spreadsheet can be downloaded via RELMA® the LOINC browser program (See Figure 3). Go to the search page and type in its name (or part of it) or its LOINC number. In Figure 3 the user typed in “master” and the browser pulled the three LOINC variables with “master” in their name. Highlight LOINC term 81247-9, then right click to get the menu that shows in the figure. Click on “Export Full panel structure to Excel.” The program will ask for a file name and store the spreadsheet on your local drive.

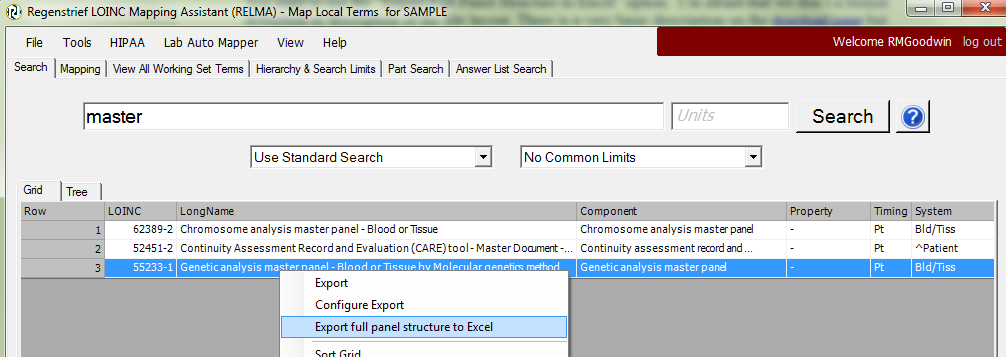


Figure 3: Screenshot of Regenstrief LOINC Mapping Assistant (RELMA) PROGRAM

Be aware that the June 2016 release 2.56 version of LOINC does not yet include all the changes made to the terms and answer lists as this guide describes. Although you can download it to play with it, please do not use it to configure your system until we get ballot feedback and get the final changes into the LOINC database, around the end of December 2016.

## More about the change from the use of OBR–OBX nesting to OBX-4 dot notation and its implementation

The 2013 HL7 V2 Clinical Genomics implementation guide included a number of nested LOINC panels. It used nested OBR-OBX relationships to represent that nesting in the message. The HL7 Clinical Genomics Work Group thought that it would probably be easier to represent that nesting in OBX-4 using dot notation (like a Dewey decimal), which also conforms with LRI. So that is how we have implemented it. The message is still defined by a hierarchy of panels (as shown in the example/definition). But the message contains just one OBR, which will carry the code for the order code. The panel structure in LOINC will define the message structure but the message will not include OBRs carrying the panel IDs as was the case for the 2013 message.

**Balloters please opine on whether we should stay with this approach or re-consider the OBR–OBX structure. Also if there are better OBX-4 dot numbering systems, suggest them.**

Recall that within one OBR panel no two OBX’s should contain the same identifier (OBX-3) and the same string in OBX-4. If all OBXs have distinct Observation IDs, OBX-4 is not required to distinguish them but might still serve as a grouper.

The current proposal for the OBX-4 dot notation is as follows: the OBX-4 fields for each report section will contain a string that begins with the section number, (i.e. with 2, 3, 4, or 5) for simple, structural, pharmacogenomic and complex variants respectively. If the panels in a section could repeat the OBX-4s in each panel would increment with each repeat. So the OBX-4s in the first panel would carry n.1 the second n.2, the third n.3 -- where n is the section number. When any individual LOINC code within a panel *could* repeat (such as is true in Table 2 Rows A.3 and A.6). Then add another level to the string. For example 1.1.1, 1.1.2, 1.2.3. If more than one individual LOINC within a panel could repeat, the two would carry the same sequence of values (e.g. 1.1.1, 1.1.2) but that does not cause a problem because the LOINC code within this panel would distinguish (and group) the repeats within a panel. (We encourage using the option of storing multiple values separated by tilde in one field, so you can avoid that extra level of repeats in most cases).

When a child panel is nested inside of a parent panel as occurs in report section 4 (pharmacogenomics) and section 5 (complex variants), one adds a level to the dot notation for each new subsumed child panel. So all of the OBX-4s in the first panel at the first level in section 4 would be valued with 4.1, those in the second panel at the first level would be valued with 4.2. The OBX-4s of the child panels within the first parent panel would carry 4.1.1 those in the 2nd child panel would carry 4.1.2, and so on. To see a specific instance, see the example in Table 5, which shows reports on multiple genes (the first panel level in each of which reports interpretations about multiple drugs).

We developed it this way to provide linkage that could cross reference all of the terms in a panel even when we do not have an OBR at the head of the panel (e.g. for the genotype star notations).

# Example Genetic report messages in V2 Syntax

## Our approach to example messages: General Notes

In this section we present example V2 messages to illustrate the use of this specification for a variety of different genetic tests. We present these example messages in shortened form leaving out the early segments like MSH and PID, which will not change across the examples, and have only populated the most important payload fields of the OBX segments, i.e., OBX-1 through OBX-6). We simplified them this way so the reader could focus on the salient features of the examples

We put the example message of the variants in the order of the five sections of the clinical genetics report – Table 2 through Table 6. Please note that there are multiple examples for each variant, with each example addressing the different ways to report the kind of variant. The example messages were taken from published sample reports, and we would like to thank the vendors who posted example reports with positive findings on the web.

The examples are all based on the content of real but anonymized narrative reports from various genetic testing services and /or content from submission to NCBI. So they will be internally consistent. The narrative laboratory reports from which many of these were derived did not always carry everything (e.g. reference sequences) that this guide considers important, so that information may be missing

We generated most of the message content by entering the data for each of the observation into the LHC-Form for this guide and created draft examples by evoking the Form’s HL7 message generating option (<https://lforms-demo.nlm.nih.gov/>). As of late July 2016, the draft example messages do not yet match the specification in this guide. For example, the current LHC-Forms program emits OBR segments for each panel (which it shouldn’t) and does not use the prescribed rule for generating OBX-4 values and more. We bring this up to alert users who may try out the example messages function of LHC-Forms. These errors will be fixed by the end of August.

We corrected these errors in the examples with hand editing. We also added some formatting that is not native to the LHC-Forms sample message generator. For example, we bolded the three letter segment identifier, the name of the variable (in OBX-3), and the name of the answer (in OBX-5), to make the meaning stand out from all of the coding. We used red to highlight the OBX-4 values to make the hierarchy more visible. When a single OBX wrapped to two or more lines, we indented the wrapped text. We also specialized the coding systems within the list of “mutations tested for” to reflect the varying use of c.HGVS and p.HGVS and full ClinVar names in the examples. The sample message system is not smart enough to do that and will only be able to blindly insert “HGVS” as the general coding system.

In the example messages, codes that need new LOINCs are labeled “Pending LOINC #”, e.g. Medication usage suggestion [narrative]” is “Pending LOINC 2”.

In LOINC 81254-5 “Genomic allele start-end”, when the variation is at a single locus, the start-end locations of the allele are the same measure. In this case, we report the location as both the start-end, e.g. “37070354^37070354” to show the locations are the same. The data type also allows you to report the location as a single base, e.g. “37070354.”

For LOINC 69551-0 “Genomic alt allele,” we report “-” when the alt allele is absent, as recommended by the Variant Call Format from IGSR: The International Genome Sample Resource.

Note that in a complex variant example, some alleles are submitted with a complex variant as one package, and do not yet have variant IDs. In this case, for the LOINC 81252-9 “Simple Variant” field, use the allele ID for the simple variants inside the complex variant, rather than the variant ID. Variant IDs will be out shortly, but not in time for this release of the guide.

For all simple variant examples, the variant ID is used in the LOINC 81252-9 “Simple Variant” field.

We added explanatory comments in blue font between some of the message segments. These are distinguished from the real message content by leading and trailing asterisks, e.g.:\*\*\* Comment \*\*\*.

## Simple Variant Example Messages

### Simple Variant, Example of mutation analysis of one gene by sequencing

*Note(s):*

The narrative text was invented based on a sample report on Galactosemia Gene Analysis, which tested for 14 mutations. A heterozygous and known pathogenic variation was identified, which indicated the individual may be a carrier for galactosemia.

Note that for one of the mutations tested for – the 5 kb deletion – we coded it as text in CWE.9 with ^^^^^^^^ because as described, it does not fit the coding system syntax. The mutation is found in ClinVar as part of a haplotype, 126453^[NM\_000155.2(GALT):c.1039\_753del][NM\_000155.2(GALT):c.820+50\_\*789delinsGAATAGACCCCA. The report only studies NM\_000155.2(GALT):c.1039\_753del, the 5kb deletion portion.

**OBR**|1|Acme23469|Gen825750|76037-1^GALT gene full mutation analysis in Blood or Tissue by Sequencing Narrative^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*  
**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient may be carrier for classic galactosemia.|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^LN**|1|**C0016952^**Galactosemia**^MedGen-Dis|

**OBX|**3|x|Pending LOINC 1^**Default transcript reference sequence**^RefSeq-T**|1|**

NM\_000249^**NM\_000249**^ RefSeq-T|

**OBX|**4|CNE|48018-6^**Gene(s) assessed**^LN**|1.1|**4135^**GALT**^HGNC-Symb|

**OBX|**5|CWE|36908-2^**Gene mutations tested**^LN**|1.1|**-119\_-116delGTCA^**-119\_-116delGTCA**^HGVS.c~

Asp98Asn^**Asp98Asn**^HGVS.p~ Ser135Leu^**Ser135Leu**^HGVS.p~ Thr138Met^**Thr138Met**^HGVS.p~ Met142Lys^**Met142Lys** HGVS.p~ Phe17Ser^**Phe17Ser**^HGVS.p~ Gln188Arg^**Gln188Arg**^HGVS.p~ Leu195P^**Leu195P**^HGVS.p~ Y209C^**Y209C**^HGVS.p~ Lys285Asn^**Lys285Asn**^HGVS.p~ **Asn314Asp**^Asn314Asp^HGVS.p~ Gln355Lys^**Gln355Lys**^HGVS.p~ 253-2A>G^**253-2A>G**^HGVS.c~ ^^^^^^^^5 kb deletion *(126453^[NM\_000155.2(GALT):c.-1039\_753del][NM\_000155.2(GALT):c.820+50\_\*789delinsGAATAGACCCCA]^ClinVar-V*|

**OBX|**6|CNE|51968-6^**Discrete variation analysis overall interpretation**^LN|1|LA6576-8^**Positive**^LN|

**OBX|**7|TX|51969-4^**Full narrative report**^LN**|1| Result Summary**- Positive~~ **Result** – The following heterozygous

alteration was identified: Amino Acid change: p.Q188R (Gln188Arg). DNA change: c.563A>G (g.34648167). Classification: PATHOGENIC ~~ **Interpretation -** Biochemical and molecular test results are in

agreement. The observed GALT enzyme activity in red blood cells (12.2 nmol/h/mg Hb) and the presence of a single copy of p.Q188R suggest that this individual is a carrier of classic galactosemia. This individual should not be at risk for developing symptoms related to this disorder; however, he or she may be at risk for having offspring with galactosemia. If appropriate, enzymatic and molecular studies for this individual's reproductive partner are recommended to further clarify this risk. ~~ **Method**  - A multiplex PCR-based assay was used to test for the presence of the following mutations in the GALT gene.|

\*\*\* Technical details\*\*\*

**OBX|**8|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029-5^**GRCh37**^LN|  
**OBX|**9|NM|82115-7^**dbSNP version**^LN**|1|147**|

\*\*\*Attributes of Simple Genetic Variants: Report Section 2\*\*\*  
**OBX|**10|CNE|81252-9^**Simple variant**^ClinVar-V**|1.1|**3614^**NM\_000155.3(GALT):c.563A>G**

**(p.Gln188Arg)**^ClinVar-V|  
 \*\*\*Transcript Specification Variables\*\*\*  
**OBX|**11|CWE|48018-6^**Gene studied**^HGNC-Symb**|2.1|**3614^**GALT**^HGNC-Symb|  
**OBX|**12|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|2.1|**NM\_000155.3^**NM\_000155.3**^RefSeq-T|  
**OBX|**13|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.1|** c.563A>G^**c.563A>G**^HGVS.c|  
**OBX|**14|CWE|48005-3^**Amino acid change p.HGVS**^HGVS.p**|2.1|**p.Gln188Arg^**p.Gln188Arg**^HGVS.p|  
**OBX|**15|CWE|48019-4^**DNA change type**^LN**|2.1|** LA6690-7^**Substitution** ^LN|  
**OBX|**16|CWE|48006-1^ LA6690-7^**Substitution** ^LN**|2.1|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**17|CWE|48013-7^**Genomic reference sequence**^RefSeq-G**|2.1|**NC\_000009.11^**NC\_000009.11**^RefSeq-G|  
**OBX|**18|ST|69547-8^**Genomic ref allele**^LN**|2.1|A**|  
**OBX|**19|NR|81254-5^**Genomic allele start-end**^LN**|2.1|34648167**^**34648167**|  
**OBX|**20|ST|69551-0^**Genomic alt allele**^LN**|2.1|G**|  
 \*\*\*Other variables\*\*\*  
**OBX|**21|CNE|81255-2^**dbSNP ID**^dbSNP**|2.1|** rs75391579^**rs75391579**^dbSNP|  
**OBX|**22|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.1|**9p13^**9p13**^Chrom-Loc|  
**OBX|**23|CNE|48002-0^**Genomic source class**^LN**|2.1|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**24|CNE|53037-8^**Clinical significance**^LN**|2.1|**LA6668-3^**Pathogenic**^LN|  
**OBX|**25|CWE|81259-4^**Probable associated phenotype**^LN**|2.1|**C0268151^**Deficiency of UDPglucose-hexose-1-**

**phosphate uridylyltransferase**^MedGen-Dis|  
 \*\*\*Allelic state/phase information\*\*\*  
**OBX|**26|CNE|53034-5^**Allelic state**^LN**|2.1|**LA6706-1^**Heterozygous**^LN|

### Simple Variant, Example of Targeted Mutations Analysis that studies many mutations (106)

*Note(s):*

We took this example from a published sample report on Cystic Fibrosis Analysis, which tested for 106 mutations. A heterozygous and known pathogenic variation was identified, which indicated the individual may be a carrier for cystic fibrosis.

Note that in LOINC 36908-2 “Gene mutations tested,” the first four listed mutations were named in the original report as pure HGVS strings without the reference sequence and used the older amino acid representation as follows: deltaF508, delta I507, W1282X (TGG>TGA), 621+1G>T. In this example, we replaced the first form with ClinVar variant IDs. We also replaced all of the amino acid one letter abbreviations as existed in the source material to three letter abbreviations as required by today’s HGVS. Note that for some of the variations, the text reported an amino acid change to “X” as in G542X, which represents a nonsense mutation with the “X” signaling a terminate code. In the three letter conversion, you can use a “\*” or “Ter” in place of the “X.” Here, we used a “Ter,” e.g. “Gly542Ter.”

We included the full HGVS expression and ClinVar ID just to show how a full expression in the list of mutations targeted would look and to illustrate the fact that different coding systems can be used for different elements in the list. The other mutations listed depend on the “Default transcript reference sequence” for their reference sequence, and are a mix of HGVS.c, HGVS.p and raw text, which is the Exception referenced in the “Coding with Exception” data type. In the current laboratory standard, non-coded insertions (text) goes into CWE.9 – the “original text” field. Be aware that some in the V2 community believe it should go into CWE.2 – with nulls in CWE.1 and CWE.3. Because this is a laboratory message, we used the CWE.9 convention. A case in point is “the deletion of exons 2-3” recorded as “^^^^^^^^the deletion of exons 2-3”.

We also treat the few mutations in this example that describe both protein and coding variations, e.g. “Ser466Ter (C>A)” as text and show them in CWE.9.

In this example we show the list of mutations tested for as a list in one OBX which echoes the way they are often listed separated by comma’s or semicolons in a narrative report. These *could* also be reported each in its own OBX, with increments in the OBX-4.

As per the guide, in this example, we populate both CWE.1 and CWE.2 with the same string when the coding system does not have a name (print string) that is distinct from the code.

**Balloters: Please comment on the proposal to record the same content in CWE.1 and CWE.2 when a code has no separate name or the name has no separate code. This seemed the most consistent and least complicated for the receiver but the example may be more difficult to read.**

Also, for LOINC 69551-0 “Genomic alt allele,” we report “-” when the alt allele is absent as recommended by the Variant Call Format from IGSR: The international Genome Sample Resource.

**OBR**|1|Acme23469|Gen825750|38404-0^CFTR gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*

**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient may be carrier for cystic fibrosis|

**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^MedGen-Dis**|1|**

C0010674^**Cystic fibrosis**^MedGen-Dis|

**OBX|**3|CWE|Pending LOINC 1^**Default transcript reference sequence**^RefSeq-T**|1|**

NM\_000492.3^**NM\_000492.3**^RefSeq-T

**OBX|**4|CNE|48018-6^**Gene(s) assessed**^HGNC-Symb **|1.1|**1884^CFTR^HGNC-Symb|

**OBX|**5|CWE|36908-2^**Gene mutations tested**^LN**|1.1|**

7105^NM\_000492.3(CFTR):c.1521\_1523delCTT (p.Phe508delPhe)^ **7105^NM\_000492.3(CFTR):c.1521\_1523delCTT (p.Phe508delPhe)**^ClinVar-V~

7106^NM\_000492.3(CFTR):c.1519\_1521delATC (p.Ile507del)^ **7106^NM\_000492.3(CFTR):c.1519\_1521delATC (p.Ile507del)**^ClinVar-V~ 7129^NM\_000492.3(CFTR):c.3846G>A (p.Trp1282Ter)^**7129^NM\_000492.3(CFTR):c.3846G>A (p.Trp1282Ter)**^ClinVar-V~ 38799^NM\_000492.3(CFTR):c.489+1G>T^ **38799^NM\_000492.3(CFTR):c.489+1G>T**^ClinVar-V~ Gly542Ter^**Gly542Ter**^HGVS.p~Gly85Glu^**Gly85Glu**^HGVS.p~ Arg117His^**Arg117His**^HGVS.p~ 711+1G>T^**711+1G>T**^HGVS.c ~ ^^^^^^^^**Asn1303Lys (C>A)**~ Arg334Trp^ **Arg334Trp**^HGVS.p~ Arg347Pro^**Arg347Pro**^HGVS.p ~ Ala455Glu^**Ala455Glu**^HGVS.p~ 17171G>A^**17171G>A**^HGVS.c~^^^^^^^^**Ala1303Lys (C>G)**~ Arg553Ter^**Arg553Ter**^HGVS.p~ Arg560Thr^**Arg560Thr**^HGVS.p~ Gly551Asp^**Gly551Asp**^HGVS.p~ 1898+1G>A^**1898+1G>A**^HGVS.c~ 2184delA^**2184delA**^HGVS.c~ 2789+5G>A^**2789+5G>A**^HGVS.c **~** 3120+1G>A^**3120+1G>A**^HGVS.c~ Arg1162Ter^**Arg1162Ter**^HGVS.p~ 3659delC^**3659delC**^HGVS.c~ 3849+10kbC>T^**3849+10kbC>T**^HGVS.c~ ^^^^^^^^**the deletion of exons 2-3**~ 296+2T>A^**296+2T>A**^HGVS.c~ Glu60Ter^**Glu60Ter**^HGVS.p~ Arg75Ter^**Arg75Ter**^HGVS.p~ 394\_395delTT^**394\_395delTT**^HGVS.c~ 405+1G>A^**405+1G>A**^HGVS.c ~ 406-1G>A^**406-1G>A**^HGVS.c~ Glu92Ter^**Glu92Ter**^HGVS.p~ 444delA^**444delA**^HGVS.c~ 456TAT>G^**456TAT>G**^HGVS.c~ Arg117Cys^**Arg117Cys**^HGVS.p~ Tyr122Ter^**Tyr122Ter**^HGVS.p~ 574delA^**574delA**^HGVS.c~ 663delT^**663delT**^HGVS.c~ Gly178Arg^**Gly178Arg**^HGVS.p~ 711+5G>A^**711+5G>A**^HGVS.c~ 712-1G>T^**712-1G>T**^HGVS.c~ His199Tyr^**His199Tyr**^HGVS.p~ Pro205Ser^**Pro205Ser**^HGVS.p~ Leu206Trp^**Leu206Trp**^HGVS.p~ 852del22^**852del22**^HGVS.c~ 935delA^**935delA**^HGVS.c~ 936delTA^**936delTA**^HGVS.c~ ^^^^^^^^**deltaF311**~ 1078delT^**1078delT**^HGVS.c~ Gly330Ter^**Gly330Ter**^HGVS.p~Thr338Ile^**Thr338Ile**^HGVS.p~ Arg347His^**Arg347His**^HGVS.p~ Arg352Gln^**Arg352Gln**^HGVS.p~ Gln359Lys^**Gln359Lys**^HGVS.p~ T360Lys^**T360Lys**^HGVS.p~ 1288insTA^**1288insTA**^HGVS.c~ ^^^^^^^^**Ser466Ter (C>A)**~ ^^^^^^^^**Ser466Ter (C>G)**~ G480C^**G480C**^HGVS.p~ Gln493Ter^**Gln493Ter**^HGVS.p~ 1677delTA^**1677delTA**^HGVS.c~ Cys524Ter^**Cys524Ter**^HGVS.p~ Ser549N^**Ser549N**^HGVS.p~ ^^^^^^^^**Ser549Arg (T>G)**~ Gln552Ter^**Gln552Ter**^HGVS.p~ Ala559Thr^**Ala559Thr**^HGVS.p~ 1811+1.6kbA>G^**1811+1.6kbA>G**^HGVS.c~ 1812-1G>A^**1812-1G>A**^HGVS.c~ 1898+1G>T^**1898+1G>T**^HGVS.c~ 1898+1G>C^**1898+1G>C**^HGVS.c~ 1898+5G>T^**1898+5G>T**^HGVS.c~ Pro574His^**Pro574His**^HGVS.p~ 1949del84^**1949del84**^HGVS.c~ 2043delG^**2043delG**^HGVS.c~ 2055del9>a^**2055del9>a**^HGVS.c~ 2105del13ins5^**2105del13ins5**^HGVS.c~ 2108delA^**2108delA**^HGVS.c~ 2143delT^**2143delT**^HGVS.c~ 2183\_2184delAAinsG^**2183\_2184delAAinsG**^HGVS.c~ 2184insA^**2184insA**^HGVS.c~ Arg709Ter^**Arg709Ter**^HGVS.p~ Lys710Ter^**Lys710Ter**^HGVS.p~ 2307insA^**2307insA**^HGVS.c~ Arg764Ter^**Arg764Ter**^HGVS.p~ Gln890Ter^**Gln890Ter**^HGVS.p~ 2869insG^**2869insG**^HGVS.c~ 3171delC^**3171delC**^HGVS.c~ 3199del6^**3199del6**^HGVS.c~ Arg1066Cys^**Arg1066Cys**^HGVS.p~ ^^^^^^^^**Trp1089Ter (TGG>TAG)**~ ^^^^^^^^**Tyr1092Ter (C>G)**~ ^^^^^^^^**Tyr1092Ter (C>A)**~ Met1101Lys^**Met1101Lys**^HGVS.p~ Met1101Arg^**Met1101Arg**^HGVS.p~ Asp1152His^**Asp1152His**^HGVS.p~ Arg1158Ter^**Arg1158Ter**^HGVS.p~ **3667del4**^HGVS.c~ Ser1196Ter^**Ser1196Ter**^HGVS.p~ ^^^^^^^^**Trp1204Ter (TGG>TAG)**~ 3791delC^**3791delC**^HGVS.c~ Gln1238Ter^**Gln1238Ter**^HGVS.p~ 3876delA^**3876delA**^HGVS.c~ Ser1251Asn^**Ser1251Asn**^HGVS.p~ Ser1255Ter^**Ser1255Ter**^HGVS.p~ 3905insT^**3905insT**^HGVS.c~ 4016dupT^**4016dupT**^HGVS.c|

**OBX|**6|CNE|51968-6^**Discrete variation analysis overall interpretation**^LN|1|LA6576-8^**Positive**^LN|

**OBX|**7|TX|51969-4^**Full narrative report**^LN**|1|Result Summary-** Positive. ~~ **Result**- he following heterozygous

sequence change was identified. Amino Acid: p.F508del (Phe508del), DNA change: c.1521\_1523delCTT (g.117199646\_117199648), Classification: Pathogenic. ~~ **Interpretation**-This result indicates that this

individual is a carrier of cystic fibrosis (CF). This interpretation assumes that this individual is not clinically affected with CF. Since a mutation has been identified, genetic testing of at risk family members could be considered. If appropriate, genetic testing should be offered to this individual's reproductive partner to further clarify their risk of having a child with CF. ~~ **Method**- A multiplex PCR based was used to detect 106 mutations, including the 23 mutations specified in the American College of Medical Genetics (ACMG) standards for population based carrier screening…Poly T determination and confirmatory testing of homozygous results are performed as reflex tests when appropriate.|

\*\*\*\* Technical details\*\*\*

**OBX|**8|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029-5^**GRCh37**^LN|  
**OBX|**9|NM|82115-7^**dbSNP version**^LN**|1|147**|

\*\*\*Attributes of Simple Genetic Variants: Report Section 2\*\*\*

**OBX|**10**|**CNE|81252-9^Simple variant^ClinVar-V**|2.1|**

**7105^NM\_000492.3(CFTR):c.1521\_1523delCTT (p.Phe508delPhe)**^ClinVar-V|

\*\*\*Transcript Specification Variables\*\*\*  
**OBX|**11|CWE**|**48018-6^**Gene studied**^HGNC-Symb**|2.1|**1884^**CFTR**^HGNC-Symb|  
**OBX|**12|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|2.1|**

NM\_000492.3^**NM\_000492.3**^RefSeq-T|  
**OBX|**13|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.1|**

c.1521\_1523delCTT^**c.1521\_1523delCTT**^HGVS.c|  
**OBX|**14|CWE|48005-3^**Amino acid change p.HGVS**^HGVS.p**|2.1|**

p.Phe508delPhe^**p.Phe508delPhe**^HGVS.p|  
**OBX|**15|CWE|48019-4^**DNA change type**^LN**|2.1|**LA6692-3l^**deletion**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*

**OBX|**16|CWE|48013-7^**Genomic reference sequence**^RefSeq-G **|2.1|**

NC\_000007.13^**NC\_000007.13**^RefSeq-G|

**OBX|**17|ST|69547-8^**Genomic ref allele**^LN**|2.1|CTT**|  
**OBX|**18|NR|81254-5^**Genomic allele start-end**^LN**|2.1|117199646**^**117199648**|  
**OBX|**19|ST|69551-0^**Genomic alt allele**^LN**|2.1|-**|

\*\*\*Other variables\*\*\*

**OBX|**20|CNE|81255-2^**dbSNP ID**^dbSNP**|2.1|**rs113993960^**rs113993960**^dbSNP|  
**OBX|**21|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.1|**7q31.2^**7q31.2**^Chrom-Loc|  
**OBX|**22|CNE|48002-0^**Genomic source class**^LN**|2.1|**LA6683-2^**Germline**^LN|

\*\*\*Interpretations\*\*\*  
**OBX|**23|CNE|53037-8^**Clinical significance**^LN**|2.1|**LA6668-3^**Pathogenic**^LN|  
**OBX|**24|CNE|69548-6^**Genomic variant assessment**^LN**|2.1|**LA9633-4^**Present**^LN|  
**OBX|**25|CWE|81259-4^**Probable associated phenotype**^MedGen-Dis**|2.1|** C0010674^**Cystic**

**fibrosis**^MedGen-Dis|

\*\*\*Allelic state/phase information\*\*\*  
**OBX|**26|CNE**|**53034-5^**Allelic state**^LN**|2.1|**LA6706-1^**Heterozygous**^LN|

### Simple Variant, Example of mutation analysis with sequence plus Deletion-duplication study

*Note(s):*

We took this example from a published sample report on a full gene analysis for MLH1. A heterozygous and known pathogenic variation was identified, which resulted in a diagnosis of Lynch Syndrome.

Note that in this example, the HGVS expression in LOINC 81252-9 “Simple variant” includes “Profs” which references Proline and a frameshift variation (we were not familiar with this notation, but found it in the HGVS manual).

**OBR**|1|Acme23469|Gen825750|38536-9^MLH1 gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*

**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient may have Lynch Syndrome|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^MedGen-Dis**|1|**C0009405^**Lynch**

**syndrome**^MedGen-Dis|  
**OBX|**3|CWE|Pending LOINC 1^**Default transcript reference sequence**^RefSeq-T **|1|**

NM\_000249^**NM\_000249**^RefSeq-T|

**OBX|**4|CNE|48018-6^**Gene(s) assessed**^HGNC-Symb**|1.1|**7127^**MLH1**^HGNC-Symb|

**OBX|**5|TX|81293-3^**Description of ranges of DNA sequences examined**^LN**|1|**Bi-directional

sequence analysis was performed to test for the presence of a mutation in all coding regions

and intron/exon boundaries of the MLH1 gene.|  
**OBX|**7|CNE|51968-6^**Discrete variation analysis overall interpretation**^LN|1|LA6576-8^**Positive**^LN|

**OBX|**8|CWE|Pending LOINC 2^**Deletion-duplication overall interpretation**^LN|1|Answer code pending^**No deletion duplications detected in studied regions**^LN|

**OBX|**9|TX|51969-4^**Full narrative report**^LN**|1|Result Summary**- Positive~~ **Result**- The following heterozygous

alteration was identified: Amino Acid change: p.R497PfsX6 (Arg497ProfsX6) DNA change: c.1489dupC (g.37070354) Classification: PATHOGENIC. ~~ **Interpretation** - The c.1489dupC (p.R497PfsX6)

alteration is a known pathogenic mutation. This result is consistent with a diagnosis of Lynch

syndrome for this individual. ~~ **Method –** Bi-directional sequence analysis

was performed to test for the presence of a mutation in all coding regions and intron/exon

boundaries of the MLH1 gene. Array comparative genomic hybridization (aCGH) was used to test for the presence of large deletions and duplications in this gene.|

\*\*\* Technical details\*\*\*

**OBX|**10|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029-5^**GRCh37**^LN|  
**OBX|**11|NM|82115-7^**dbSNP version**^LN**|1|147**|

\*\*\*Attributes of Simple Genetic Variants: Report Section 2\*\*\*  
**OBX|**12|CNE|81252-9^**Simple variant**^ClinVar-V**|2.1|**89753^**NM\_000249.3(MLH1):c.1489dupC**

**(p.Arg497Profs)**^ClinVar-V|  
 \*\*\*Transcript Specification Variables\*\*\*  
**OBX|**13|CWE|48018-6^**Gene studied**^HGNC-Symb**|2.1|**89753^**MLH1**^HGNC-Symb|  
**OBX|**14|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|2.1|**

NM\_000249.3^**NM\_000249.3**^RefSeq-T|  
**OBX|**15|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.1|**c.1489dupC^**c.1489dupC**^HGVS.c|  
**OBX|**16|CWE|48005-3^**Amino acid change p.HGVS**^ HGVS.p **|2.1|**

p.Arg497Profs^**p.Arg497Profs**^HGVS.p|  
**OBX|**16|CWE|48019-4^**DNA change type**^LN**|2.1|**LA6686-5^**Duplication**^LN|  
**OBX|**17|CWE|48006-1^**Amino acid change type**^LN**|2.1|**LA6694-9^**Frameshift**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**18|CWE|48013-7^**Genomic reference sequence**^RefSeq-G**|2.1|**

NC\_000003.11^**NC\_000003.11**^RefSeq-G|  
**OBX|**19|ST|69547-8^**Genomic ref allele**^LN**|2.1|C**|  
**OBX|**20|NR|81254-5^**Genomic allele start-end**^LN**|2.1|37070354**^**37070354**|  
**OBX|**21|ST|69551-0^**Genomic alt allele**^LN**|2.1|CC**|  
 \*\*\*Other variables\*\*\*

**OBX|**22|CNE|81255-2^**dbSNP ID**^dbSNP**|2.1|**rs63751031^**rs63751031**^dbSNP|  
**OBX|**23|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.1|**

3p22.2^**3p22.2**^Chrom-Loc|  
**OBX|**24|CNE|48002-0^**Genomic source class**^LN**|2.1|**LA6683-2^**Germline**^LN|

\*\*\*Interpretations\*\*\*  
**OBX|**25|CNE|53037-8^**Clinical significance**^LN**|2.1|**LA6668-3^**Pathogenic**^LN|  
**OBX|**26|CNE|69548-6^**Genomic variant assessment**^LN**|2.1|**LA11884-6^**Indeterminate**^LN|  
**OBX|**27|CWE|81259-4^**Probable associated phenotype**^LN**|2.1|**C0009405^**Lynch**

**syndrome**^MedGen-Dis|  
 \*\*\*Allelic state/phase information\*\*\*  
**OBX|**28|CNE|53034-5^**Allelic state**^LN**|2.1|**LA6706-1^**Heterozygous**^LN|

### Simple Variant, Example of multi-gene mutation analysis and Duplication-deletion study.

*Note(s):*

We took this example from a published example report, but one of the reported variants is not necessarily clinically important, and was not reported in NCBI’s ClinVar.

Also, the report lists the variant NM\_007254.3(PNKP):c.188C>T (p.Ala63Val) as a likely benign variant, but ClinVar describes the variant as having uncertain clinical significance, and links the variant to a probably associated phenotype of Early infantile epileptic encephalopathy 10, which is how we reported the clinical significance.

**OBR**|1|Acme23469|Gen825750| **35693-1^GBA gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative^LN**|R|201608030830|201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*  
**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient may have infantile epilsepy.|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^LN**|1|**C0268126^**Adenylosuccinate lyase deficiency**^MedGen-

Dis~ C0162635^**Angelman syndrome**^MedGen-Dis~ CN128785^**Angelman syndrome-like**^MedGen-Dis~ C2748910^**Atypical Rett syndrome**^MedGen-Dis~ C1843140^**Benign familial neonatal-infantile seizure**s^MedGen-Dis~ C2930911^**Benign familial neonatal seizures**^MedGen-Dis~ CN227588^**Cerebral creatine deficiency syndrome**^MedGen-Dis~ C0393706^**Early infantile epileptic encephalopathy**^MedGen-Dis~ C3150667^**Early infantile epileptic encephalopathy 10**^MedGen-Dis~ CN220161^**Infantile spasms**^MedGen-Dis~ C3502809^**Generalized epilepsy with febrile seizures plus**^MedGen-Dis~ C1847501**^Glucose transporter type 1 deficiency syndrome**^MedGen-Dis~ C1856113^**Mowat-Wilson syndrome**^MedGen-Dis~ C1849508^**Pyridoxine-dependent epilepsy**^MedGen-Dis~ CN221284^**Encephalopathy, neonatal severeMental retardation, X-linked, syndromic 13Rett syndrome**^MedGen-Dis~ C0037769^**West syndrome**^MedGen-Dis|

**OBX|**3|CNE|48018-6^**Gene(s) assessed**^LN**|1.1|**291^**ADSL**^HGNC-Symb~ 877^**ALDH7A1**^HGNC-Symb~

30881^**ALG13**^HGNC-Symb~ 14561^**ARHGEF9**^HGNC-Symb~ 18060^**ARX**^HGNC-Symb~ 18305^**ATP6AP2**^HGNC-Symb~ 1388^**CACNA1A**^HGNC-Symb~ 11411^**CDKL5**^HGNC-Symb~ 1917^**CHD2**^HGNC-Symb~ 1960^**CHRNA7**^HGNC-Symb~ 2074^**CLN3**^HGNC-Symb~ 2076^**CLN5**^HGNC-Symb~ 2077^**CLN6**^HGNC-Symb~ 2079^**CLN8**^HGNC-Symb~ 13830^**CNTNAP2**^HGNC-Symb~ 2529^**CTSD**^HGNC-Symb~ 2972^**DNM1**^HGNC-Symb~ 3091^**DYRK1A**^HGNC-Symb~ 3192^**EEF1A2**^HGNC-Symb~ 3791^**FOLR1**^HGNC-Symb~ 3811^**FOXG1**^HGNC-Symb~ 4075^**GABRA1**^HGNC-Symb~ 4082^**GABRB2**^HGNC-Symb~ 4083^**GABRB3**^HGNC-Symb~ 4087^**GABRG2**^HGNC-Symb~ 4136^**GAMT**^HGNC-Symb~ 4175^**GATM**^HGNC-Symb~ 4584^**GRIN1**^HGNC-Symb~ 4585^**GRIN2A**^HGNC-Symb~ 4586^**GRIN2B**^HGNC-Symb~ 29059^**IQSEC2**^HGNC-Symb~ 24565^**KANSL1**^HGNC-Symb~ 6231^**KCNB1**^HGNC-Symb~ 6256^**KCNJ10**^HGNC-Symb~ 6296^**KCNQ2**^HGNC-Symb~ 6297^**KCNQ3**^HGNC-Symb~ 18865^**KCNT1**^HGNC-Symb~ 21957^**KCTD7**^HGNC-Symb~ 18957^**MAGI2**^HGNC-Symb~ 20444^**MBD5**^HGNC-Symb~ 6990^**MECP2**^HGNC-Symb~ 6996^**MEF2C**^HGNC-Symb~ 28486^**MFSD8**^HGNC-Symb~ 7975^**NR2F1**^HGNC-Symb~ 8008^**NRXN1**^HGNC-Symb~ 14270^**PCDH19**^HGNC-Symb~ 8957^**PIGA**^HGNC-Symb~ 23215^**PIGO**^HGNC-Symb~ 26031^**PIGV**^HGNC-Symb~ 9154^**PNKP**^HGNC-Symb~ 30260^**PNPO**^HGNC-Symb~ 9179^**POLG**^HGNC-Symb~ 9325^**PPT1**^HGNC-Symb~ 30500^**PRRT2**^HGNC-Symb~ 9751^**QARS**^HGNC-Symb~ 10585^**SCN1A**^HGNC-Symb~ 10586^**SCN1B**^HGNC-Symb~ 10588^**SCN2A**^HGNC-Symb~ 10596^**SCN8A**^HGNC-Symb~ 23089^**SLC13A5**^HGNC-Symb~ 19954^**SLC25A22**^HGNC-Symb~ 11005^**SLC2A1**^HGNC-Symb~ 11055^**SLC6A8**^HGNC-Symb~ 11079^**SLC9A6**^HGNC-Symb~ 11273^**SPTAN1**^HGNC-Symb~ 11444^**STXBP1**^HGNC-Symb~ 29203^**TBC1D24**^HGNC-Symb~ 11634^**TCF4**^HGNC-Symb~ 2073^**TPP1**^HGNC-Symb~ 12362^**TSC1**^HGNC-Symb~ 12363^**TSC2**^HGNC-Symb~ 12496^**UBE3A**^HGNC-Symb~ 28912^**WDR45**^HGNC-Symb~ 12799^**WWOX**^HGNC-Symb~ 14881^**ZEB2**^HGNC-Symb|

**OBX|**4|CNE|51968-6^**Discrete variation analysis overall interpretation**^LN|1|LA6576-8^**Positive**^LN|

**OBX|**5|CWE| Pending LOINC 2^**Deletion-duplication overall interpretation**^LN|1|Answer code pending^**No deletion duplications detected in studied regions**^LN|

**OBX|**6|TX|51969-4^**Full narrative report**^LN**|1|Result**- Heterozygous for a single PNKP mutation; Heterozygous

for a single PRRT2 mutation. No other reportable variants detected by sequencing and deletion/duplication analysis of the 75 genes included on this panel.~~ **Interpretation**: This individual is heterozygous for a novel disease-causing mutation in the PNKP gene. This gene is associated with an autosomal recessive disorder. A second mutation may exist that is undetectable by this test or this patient may incidentally be a heterozygous carrier of the PNKP mutation. The finding of a single mutation in PNKP is not sufficient to establish a diagnosis in this patient. This individual is heterozygous for a published missense variant in the PRRT2 gene. This gene is associated with autosomal dominant disorder. With the clinical and molecular information available at this time, the clinicial significance of this variant is unknown.~~ **Method** – Using genomic DNA from the submitted specimen, the coding regions and splice junctions of 51 genes (all genes listed above except for CHRNA7 and MAGI2, since only large deletions have been reported in these genes) were sequenced with pair-end reads. Capillary sequencing was used to confirm all potentially pathogenic variants. Concurrent deletion/duplication testing was performed for the genes in the panel using exon-level oligo array CGH, except for FOXG1. Confirmation of copy number changes was performed by MLPA, qPCR, or repeat array CGH analysis.~~ **Additional Information** – The test also found likely benign variants in genes KANSL1 and PNKP.|

**OBX|**7|TX|81293-3^**Description of ranges of DNA sequences examined**^LN**|1|**The sequencing component of the test includes all genes listed above except for CHRNA7 and MAGI2, since only large deletions have been reported in these genes.|

\*\*\* Technical details\*\*\*

**OBX|**8|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029-5^**GRCh37**^LN|  
**OBX|**9|NM|82115-7^**dbSNP version**^LN**|1|147**|

\*\*\*Attributes of First Simple Genetic Variants: Report Section 2\*\*\*

**OBX|**10|CNE|81252-9^**Simple variant**^ClinVar-V**|2.1|**No Variant ID^**NM\_007254.3(PNKP):c.1315C>T**

**(p.Arg439Ter)**^ClinVar-V|  
 \*\*\*Transcript Specification Variables\*\*\*  
**OBX|**11|CWE|48018-6^**Gene studied**^HGNC-Symb**|2.1|**9154^**PNKP**^HGNC-Symb|  
**OBX|**12|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|2.1|**NM\_007254.3^**NM\_007254.3**^RefSeq-T|  
**OBX|**13|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.1|**c.610C>T^**c.1315C>T**^HGVS.c|  
**OBX|**14|CWE|48005-3^**Amino acid change p.HGVS**^HGVS.p**|2.1|**p.Arg204Ter^**p.Arg439Ter**^HGVS.p|  
**OBX|**15|CWE|48019-4^**DNA change type**^LN**|2.1|** LA6690-7^**Substitution**^LN |  
**OBX|**16|CWE|48006-1^**Amino acid change type**^LN**|2.1|**LA6699-8^**Nonsense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**17|CWE|48013-7^**Genomic reference sequence**^ RefSeq-G **|2.1|**NC\_000019.9^**NC\_000019.9**^RefSeq-G|  
**OBX|**18|ST|69547-8^**Genomic ref allele**^LN**|2.1|G**|  
**OBX|**19|NR|81254-5^**Genomic allele start-end**^LN**|2.1|50367462**^**50367462**|  
**OBX|**20|ST|69551-0^**Genomic alt allele**^LN**|2.1|A**|  
 \*\*\*Other variables\*\*\*  
**OBX|**21|CNE|81255-2^**dbSNP ID**^dbSNP**|2.1|** rs796052850^**rs796052850**^dbSNP|  
**OBX|**22|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.1|**19q13.33^**19q13.33**^Chrom-Loc|  
**OBX|**23|CNE|48002-0^**Genomic source class**^LN**|2.1|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**24|CNE|53037-8^**Clinical significance**^LN**|2.1|**LA6668-3^**Pathogenic**^LN|  
**OBX|**25|CNE|69548-6^**Genomic variant assessment**^LN**|2.1|**LA9633-4^**Present**^LN|  
**OBX|**26|CWE|81259-4^**Probable associated phenotype**^MedGen-Dis**|2.1|**CN218420^**Developmental delay AND/OR other significant developmental or morphological phenotypes**^MedGen-Dis|  
 \*\*\*Allelic state/phase information\*\*\*  
**OBX|**27|CNE|53034-5^**Allelic state**^LN**|2.1|**LA6706-1^**Heterozygous**^LN|

\*\*\*Attributes of Second Simple Genetic Variants: Report Section 2\*\*\*

**OBX|**28|CNE|81252-9^**Simple variant**^ClinVar-V**|2.2|**130039^**NM\_145239.2(PRRT2):c.67G>A**

**(p.Glu23Lys)**^ClinVar-V|  
 \*\*\*Transcript Specification Variables\*\*\*  
**OBX|**29|CWE|48018-6^**Gene studied**^HGNC-Symb**|2.2|**30500^**PRRT2**^HGNC-Symb|  
**OBX|**30|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|2.2|**NM\_145239.2^**NM\_145239.2**^RefSeq-T|  
**OBX|**31|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.2|**c.67G>A^**c.67G>A**^HGVS.c|  
**OBX|**32|CWE|48005-3^**Amino acid change p.HGVS**^HGVS.p**|2.2|**p.Glu23Lys^**p.Glu23Lys**^HGVS.p|  
**OBX|**33|CWE|48019-4^**DNA change type**^LN**|2.2|** LA6690-7^**Substitution** ^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**34|CWE|48013-7^**Genomic reference sequence**^ RefSeq-G**|2.2|**NC\_000016.9^**NC\_000016.9**^RefSeq-G|  
**OBX|**35|ST|69547-8^**Genomic ref allele**^LN**|2.2|G**|  
**OBX|**36|NR|81254-5^**Genomic allele location**^LN**|2.2|29824442**^**29824442**|  
**OBX|**37|ST|69551-0^**Genomic alt allele**^LN**|2.2|A**|  
 \*\*\*Other variables\*\*\*  
**OBX|**38|CNE|81255-2^**dbSNP ID**^dbSNP**|2.2|**rs140383655^**rs140383655**^dbSNP|  
**OBX|**39|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.2|**16p11.2^**16p11.2**^Chrom-Loc|  
**OBX|**40|CNE|48002-0^**Genomic source class**^LN**|2.2|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**41|CNE|53037-8^**Clinical significance**^LN**|2.2|**LA6671-7^**Uncertain Significance**^LN|  
**OBX|**42|CNE|69548-6^**Genomic variant assessment**^LN**|2.2|**LA9633-4^**Present**^LN|  
**OBX|**43|CWE|81259-4^**Probable associated phenotype**^LN**|2.2|**C1510586^**Autism spectrum disorders**^MedGen-

Dis|  
 \*\*\*Allelic state/phase information\*\*\*  
**OBX|**44|CNE|53034-5^**Allelic state**^LN**|2.2|**LA6706-1^**Heterozygous**^LN|

\*\*\*Attributes of Third Simple Genetic Variants: Report Section 2\*\*\*

**OBX|**45|CNE|81252-9^**Simple variant**^ClinVar-V**|2.3|**205776^**NM\_001193466.1(KANSL1):c.727C>A**

**(p.Gln243Lys)**^ClinVar-V|  
 \*\*\*Transcript Specification Variables\*\*\*  
**OBX|**47|CWE|48018-6^**Gene studied**^HGNCS-Symb**|2.3|**24565^**KANSL1**^HGNC-Symb|  
**OBX|**48|CWE|51958-7^**Transcript RefSeq ID**^ RefSeq-T**|2.3|**NM\_001193466.1^**NM\_001193466.1**^RefSeq-T|  
**OBX|**49|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.3|**c.727C>A^**c.727C>A**^HGVS.c|  
**OBX|**50|CWE|48005-3^**Amino acid change p.HGVS**^HGVS.p**|2.3|**p.Gln243Lys^**p.Gln243Lys**^HGVS.p|  
**OBX|**51|CWE|48019-4^**DNA change type**^LN**|2.3|** LA6690-7^**Substitution** ^LN |  
**OBX|**52|CWE|48006-1^**Amino acid change type**^LN**|2.3|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**53|CWE|48013-7^**Genomic reference sequence**^RefSeq-G**|2.3|**NC\_000017.10^**NC\_000017.10**^RefSeq-G|  
**OBX|**54|ST|69547-8^**Genomic ref allele**^LN**|2.3|G**|  
**OBX|**55|NR|81254-5^**Genomic allele location**^LN**|2.3|44248783**^**44248783**|  
**OBX|**56|ST|69551-0^**Genomic alt allele**^LN**|2.3|T**|  
 \*\*\*Other variables\*\*\*  
**OBX|**57|CNE|81255-2^**dbSNP ID**^dbSNP**|2.3|** rs142096969^**rs142096969**^dbSNP|  
**OBX|**58|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.3|**17q21.31^**17q21.31**^Chrom-Loc|  
**OBX|**59|CNE|48002-0^**Genomic source class**^LN**|2.3|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**60|CNE|53037-8^**Clinical significance**^LN**|2.3|**LA6674-1^**Likely Benign**^LN|  
**OBX|**61|CNE|69548-6^**Genomic variant assessment**^LN**|2.3|**LA9633-4^**Presen**t^LN|  
 \*\*\*Allelic state/phase information\*\*\*  
**OBX|**62|CNE|53034-5^**Allelic state**^LN**|2.3|**LA6706-1^**Heterozygous**^LN|

\*\*\*Attributes of Fourth Simple Genetic Variants: Report Section 2\*\*\*

**OBX|**63|CNE|81252-9^**Simple variant**^ClinVar-V **|2.4|**159792^**NM\_007254.3(PNKP):c.188C>T**

**(p.Ala63Val)**^ClinVar-V|  
 \*\*\*Transcript Specification Variables\*\*\*  
**OBX|**64|CWE|48018-6^**Gene studied**^HGNC-Symb**|2.4|**9154^**PNKP**^HGNC-Symb|  
**OBX|**65|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|2.4|**NM\_007254.3^**NM\_007254.3**^RefSeq-T|  
**OBX|**66|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|2.4|**c.188C>T^**c.188C>T**^HGVS.c|  
**OBX|**67|CWE|48005-3^**Amino acid change p.HGVS**^HGVS.p**|2.4|**p.Ala63Val^**p.Ala63Val**^HGVS.p|  
**OBX|**68|CWE|48019-4^**DNA change type**^LN**|2.4|** LA6690-7^**Substitution** ^LN |  
**OBX|**69|CWE|48006-1^**Amino acid change type**^LN**|2.4|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**70|CWE|48013-7^**Genomic reference sequence**^RefSeq-G**|2.4|**NC\_000019.9^**NC\_000019.9**^RefSeq-G|  
**OBX|**71|ST|69547-8^**Genomic ref allele**^LN**|2.4|G**|  
**OBX|**72|NR|81254-5^**Genomic allele location**^LN**|2.4|50369666**^**50369666**|  
**OBX|**73|ST|69551-0^**Genomic alt allele**^LN**|2.4|A**|  
 \*\*\*Other variables\*\*\*  
**OBX|**74|CNE|81255-2^**dbSNP ID**^ dbSNP**|2.4|** rs3739173^**rs3739173**^dbSNP|  
**OBX|**75|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|2.4|**19q13.33^**19q13.33**^Chrom-Loc|  
**OBX|**76|CNE|48002-0^**Genomic source class**^LN**|2.4|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**77|CNE|53037-8^**Clinical significance**^LN**|2.4|**LA6671-7^**Uncertain Significance**^LN|  
**OBX|**78|CNE|69548-6^**Genomic variant assessment**^LN**|2.4|**LA9633-4^**Present**^LN|  
**OBX|**79|CWE|81259-4^**Probable associated phenotype**^MedGen-Dis**|2.4|**C3150667^**Early infantile epileptic encephalopathy 10**^MedGen-Dis|  
 \*\*\*Allelic state/phase information\*\*\*  
**OBX|**80|CNE|53034-5^**Allelic state**^LN**|2.4|**LA6706-1^**Heterozygous**^LN|

\*\*\*Structural Variants: Report Section 3\*\*\*  
**OBX|**81|CWE|81304-8^**Structural variant method type**^LN**|3.1|**LA26399-8^**Oligo aCGH**^LN|

## Structural Variant Example Messages

### Structural Variant – Example of whole genome study for deletion duplication

*Note(s):*

We took this example from a published sample report on a whole genome study that found a structural variant that may contribute to a phenotype of intellectual disability. The source text uses ISCN nomenclature to report the variant.

This is a whole genome study, so the build can be taken as the reference sequence.

In LOINC 82155-3 “Copy Number,” we reported “3” because the specification requires a number, but in the narrative report from which we took this example, it was reported as a “partial trisomy.”

**OBR**|1|Acme23469|Gen825750| 62375-1^Cytogenomic SNP Microarray^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*  
**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient has encephalopathy|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^LN**|1|**C1843367^**Intellectual disability**^MedGen-Dis|

**OBX|**3|TX|81293-3^**Description of ranges of DNA sequences examined**^LN**|1|**Whole genome.|

**OBX|**4|CWE|Pending LOINC 2^**Deletion-duplication overall interpretation**^LN|1|Answer code pending^**Positive**

**for deletion duplications**^LN|

**OBX|**5|TX|51969-4^**Full narrative report**^LN**|1|Genetic Results:** The cytogenomic microarray analysis indicated

that there was a gain involving chromosome 16 (1.7 Mb duplicated) within 16p13.11, suggesting partial trisomy for this region. This duplication has been reported as a risk factor for neurocognitive disorders as it appears to be enriched in children with intellectual disabilities, but is also observed, at a lower frequency, in normal individuals. ~~ **Method:** CHROMOSOMAL MICROARRAY ANALYSIS (CMA) METHODOLOGY: This CMA was performed using Affymetrix(R) Cytogenetics Whole-Genome 2.7M Array. The array offers a total of 2,141,868 markers across the entire genome, including 1,742,975 unique non-polymorphic markers, and 398,891 SNP markers.|

\*\*\* Technical details\*\*\*  
**OBX|**6|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**Pending LA Code^**NCBI36**^LN|

\*\*\*Structural Variants: Report Section 3\*\*\*  
**OBX|**7|CWE|81298-2^**Structural variant cytogenetic location**^Chrom-Loc**|3.1|**16p13.11^**16p13.11**^Chrom-Loc|  
**OBX|**8|ST|81291-7^**Structural variant ISCN**^ISCN**|3.1|**

**arr 16p13.11(14,686,844x2,14776269-16486370x3,16,494,405x2) (hg18)**^ISCN|

**OBX|**9|ST|82155-3^**Copy number**^LN**|3.1|3**|

**OBX|**10|CWE|81289-1^**DNA structural variation type**^LN**|3.1|**LA6686-5^**Duplication**^LN|  
**OBX|**11|CWE|81304-8^**Structural variant method type**^LN**|3.1|**LA26399-8^**Oligo aCGH**^LN|

### Structural Variant – Example of whole genome study for deletion duplication

*Note(s):*

We took this example from a published sample report on a whole genome study that found a structural variant that may contribute to a phenotype of developmental delay. The source text uses ISCN nomenclature to report the variant.

Note that this is a whole genome study, so the build can be taken as the reference sequence.

Also, as of August 8, the cytogenetics location table is not complete – there are no descriptions of adjacent chromosome locations, such as 4q35.1-35.2, but they will be added shortly.

As we understand, the source table for NCBI uses dashes to represent the adjacent locations, e.g. 4q35.1-35.2. The current ISCN notation does not separate the locations, e.g. 4q35.1q35.2. **Balloters, please comment on what notation is preferred.**

**OBR**|1|Acme23469|Gen825750| Pending LOINC 3^SNP Microarray Pediatric ^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*  
**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient has developmental delay.|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^MedGen-Dis **|1|**CN218420^**Developmental delay AND/OR**

**other significant developmental or morphological phenotypes**^MedGen-Dis|

**OBX|**3|TX|81293-3^**Description of ranges of DNA sequences examined**^LN**|1|**Whole genome|

**OBX|**4|CWE|Pending LOINC 2^**Deletion-duplication overall interpretation**^LN|1|Answer code pending^**Positive**

**for deletion duplications**^LN|

**OBX|**5|TX|51969-4^**Full narrative report**^LN**|1| Microarray Result**- 6.0 MB Terminal Deletion of 4Q35.1 ->

4QTER; 8.5 MB Terminal Duplication of XQ27.3 -> XQTER. ~~ **Interpretation**- Apparent unbalanced translocation derivative. The whole genome chromosome SNP microarray copy number analysis revealed a terminal 4q deletion [Flanking proximal OMIM gene: MIR510] and a terminal gain of Xq [Flanking proximal OMIM gene: IRF2] spanning the chromosomal segments listed below. These intervals include numerous OMIM annotated genes that may contribute to the patient phenotype…No other significant DNA copy number changes or copy neutral LOH were detected within our present reporting criteria in the 2,695,000 region specific SNPs.|

\*\*\* Technical details\*\*\*

**OBX|**6|CWE|62374-4^**Human reference sequence assembly**^LN**|1|** LA14029-5^**GRCh37**^LN|

\*\*\*Structural Variants: Report Section 3\*\*\*

\*\*\*Attributes of First Structural Variant\*\*\*

**OBX|**7|CWE|81298-2^**Structural variant cytogenetic location**^LN**|3.1|**4q35.1q35.2^**4q35.1q35.2**^Chrom-Loc|  
**OBX|**8|ST|81291-7^**Structural variant ISCN**^ISCN**|3.1|arr 4q35.1q35.2 (185, 135, 549-190, 957, 473)x1**^ISCN|  
**OBX|**9|ST|82155-3^**Copy number**^LN**|3.1|1**|  
**OBX|**10|CWE|81289-1^**DNA structural variation type**^LN**|3.1|**LA6692-3^**Deletion**^LN|  
**OBX|**11|CWE|81304-8^**Structural variant method type**^LN**|3.1|**LA26400-4^**SNP Array**^LN|

\*\*\*Attributes of Second Structural Variant\*\*\*

**OBX|**12|CWE|81298-2^**Structural variant cytogenetic location**^LN**|3.2|**Xq27.3q28^**Xq27.3q28**^Chrom-Loc|  
**OBX|**13|ST|81291-7^**Structural variant ISCN**^ISCN**|3.2|Xq27.3q28 (146, 734, 447-154, 943, 511)x3**^ISCN|  
**OBX|**14|ST|82155-3^**Copy number**^LN**|3.2|3**|  
**OBX|**15|CWE|81289-1^**DNA structural variation type**^LN**|3.2|**LA6686-5^**Duplication**^LN|  
**OBX|**16|CWE|81304-8^**Structural variant method type**^LN**|3.2|**LA26400-4^**SNP Array**^LN|

### Structural Variant – Example of structural variant reported as dbVar code

*Note(s):*

The narrative text was invented based on a sample report on Tay-Sach’s Disease, with the genetic details taken from NCBI’s dbVar. It has a variant ID =nsv513781, which can be found at <http://www.ncbi.nlm.nih.gov/dbvar/variants/nsv513781/#VariantClinical> .

**OBR**|1|Acme23469|Gen825750| 51773-0^HEXA gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*

**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|** Patient may have Tay-Sach's Disease|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^MedGen-Dis**|1|** C0039373^**Tay-Sachs disease**^MedGen-Dis|  
**OBX|**3|CNE|48018-6^**Gene(s) assessed**^LN|**|1.1|** 4878^**HEXA**^HGNC-Symb|

**OBX|**4|TX|81293-3^**Description of ranges of DNA sequences examined**^LN**|1|** All coding regions and intron/exon

boundaries of the HEXA gene.|

**OBX|**5|CWE|Pending LOINC 2^**Deletion-duplication overall interpretation**^LN|1|Answer code pending^**Positive**

**for deletion duplications**^LN|

**OBX|**6|TX|51969-4^**Full narrative report**^LN**|1| Result Summary**- Positive. ~~**Result**- The following structural

alteration was identified: DNA change: c.—2654\_253+5128delinsG. Genome change: g.2644\_10588del7945insG. Classification: PATHOGENIC. ~~**Interpretation** - The c.—2654\_253+5128delinsG alteration is a known pathogenic mutation. This result indicates that this individual is a carrier of Tay Sachs disease (TSD). This assumes that this individual is not clinically affected with TSD. **Method**- Bi-directional sequence analysis was performed to test for the presence of mutations in all coding regions and intron/exon boundaries of the HEXA gene.|  
\*\*\* Technical details\*\*\*

**OBX|**7|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029-5^**GRCh37**^LN|

\*\*\*Structural Variants: Report Section 3\*\*\*  
**OBX|**8|CWE|81286-7^**Structural variant ID**^dbVar-GL **|3.1|nsv513781**^**15q23-q24(chr15)**^**(72370592-**

**72378536)x1**^dbVar-GL|  
**OBX|**9|CWE|81298-2^**Structural variant cytogenetic location**^Chrom-Loc**|3.1|**15q23q24^**15q23q24**^Chrom-

Loc|  
**OBX|**10|ST|**81290-9**^**Structural variant HGVS**^HGVS.g**|3.1|NG\_009017.1:g.2644\_10588del7945insG**^HGVS.g|  
**OBX|**11|ST|81287-5^**Structural variant** **start-end**^LN**|3.1|72370592**^**72378536**|  
**OBX|**12|CWE|81289-1^**DNA structural variation type**^LN**|3.1|**LA9659-9^**Insertion/Deletion**^LN|  
**OBX|**13|NM|81300-6^**Structural variant length**^LN**|3.1|7945**|  
**OBX|**14|CWE|81304-8^**Structural variant method type**^LN**|3.1|**LA26402-0^**Curated**^LN|

## Pharmacogenomics Example Message

### Pharmacogenomics, Example of Pharmacogenomics Study of 4 genes with guidance about selected drugs nested in results for each gene

**OBR**|1|Acme23469|Gen825750|Pending LOINC 4^Multiple CYP genes & VKORC1 gene Pharmacogenomic Analysis^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*

**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|Patient not responding to drug.**|  
**OBX|**2|CWE|51963-7^**Medications assessed**^RxT-Ingrd**|1.1|**4493^**Fluoxetine**^RxT-Ingrd

~83367^**atorvastatin**^RxT-Ingrd~7258^**Naproxen**^RxT-Ingrd~11289^**Warfarin**^RxT-Ingrd ~6754^**Meperidine**^RxT-Ingrd|

**OBX|**3|CNE|48018-6^**Gene(s) assessed**^HGNC-Symb**|1.1|**2623^**CYP2C9**^HGNC-Symb~

2637^**CYP3A4**^ HGNC-Symb~ 2638^**CYP3A5**^HGNC-Symb~ 23663^**VKORC1**^HGNC-Symb~ 2625^**CYP2D6**^HGNC-Symb~ 2621^**CYP2C19**^HGNC-Symb|

**OBX|**4|TX|51969-4^**Full narrative report**^LN**|1|** **Results –** Genes CYP2C9, CYP2C9/VKORC1, and

CYP3A4/CYP3A5 have abnormal drug responses. CYP2C9 is a Poor Metabolizer for Fluoxetine and Naproxen; CYP2C9/VKORC1 is a Poor Metabolizer with High Sensitivity for Warfarin; CYP3A4/CYP3A5 is an Increased Metabolizer for Atorvastatin. Genes CYP2C19 and CYP2D6 have normal responses.~~ **Method -** Genomic DNA was extracted from the submitted specimen and amplified by the polymerase chain reaction (PCR) using consensus oligonucleotide primers specific for the following genes: CYP2C9, VKORC1, CYP3A4, CYP3A5, Factor II, Factor V Leiden, and MTHFR; assay may also include CYP2C19 and/or CYP2D6. Clinically relevant genetic variants were detected after amplification using the Luminex 100/200 Instrument|

\*\*\* Pharmacogenomics: Report Section 4\*\*\*

\*\*\* Results for first gene in the study\*\*\*  
**OBX|**5|CWE|48018-6^**Gene(s) studied**^HGNC-Symb**|4.1|**2623^**CYP2C9**^HGNC-

Symb~23663^**VKORC1**^HGNC-Symb|  
**OBX|**6|ST|47998-0^**Genotype display name**^LN**|4.1|\*2/\*5~\*A/\*A**|  
**OBX|**7|CWE|53040-2^**Genetic variation's effect on drug metabolism interp**^LN**|4.1|**LA9657-

3^**Poor metabolizer**^LN|

\*\*\*Medication usage implications panel\*\*\* **OBX|**8|CWE|51963-7^**Medication assessed**^RxT-Ingrd**|4.1.1|**11289^**Warfarin**^RxT-Ingrd|  
**OBX|**9|CWE|82116-5^**Medication usage suggestion [type]**^LN**|4.1.1|**LA26425-1^**Use**

**Caution**^LN|  
**OBX|**10|TX|Pending LOINC 2^**Medication usage suggestion [narrative**]^LN**|4.1.1|**Consider 0.5-2 mg/day to

achieve therapeutic INR using the warfarin product insert approved by the USFDA.|

\*\*\* Results for second gene in the study\*\*\*

**OBX|**11|CWE|48018-6^Gene(s) studied^LN**|4.2|**2623^**CYP2C9**^HGNC-Symb|  
**OBX|**12|ST|47998-0^**Genotype display name**^LN**|4.2|**\***2/\*5**|  
**OBX|**13|CWE|53040-2^**Genetic variation's effect on drug metabolism interp**^LN**|4.2|**LA9657-

3^**Poor metabolizer**^LN|  
 \*\*\*Medication usage implications panel\*\*\*  
**OBX|**14|CWE|51963-7^**Medication assessed**^RxT-Ingrd**|4.2.1|**4493^**Fluoxetine**^RxT-Ingrd|  
**OBX|**15|CWE|82116-5^**Medication usage suggestion [type]**^LN**|4.2.1|**LA26421-0^**Consider**

**Alternative Medication**^LN|  
**OBX|**16|TX|Pending LOINC 2^**Medication usage suggestion [narrative]**^LN**|4.2.1|**Monitor for inhibition of

other drugs. Fluoxetine is a strong 2D6 inhibitor and is known to effect drugs which use the

CYP 2D6 pathway.|  
 \*\*\*Medication usage implications panel\*\*\*  
**OBX|**17|CWE|51963-7^**Medication assessed**^RxT-Ingrd**|4.2.2|**7258^**Naproxen**^RxT-Ingrd|  
**OBX|**18|CWE|82116-5^**Medication usage suggestion [type]**^LN**|4.2.2|**LA26424-4^**Use**

**Caution**^LN|  
**OBX|**19|TX|Pending LOINC 2^**Medication usage suggestion [narrative]**^LN**|4.2.2|**Consider Dosage

reduction. Monitor for Gastrointestinal Bleeding.|

\*\*\* Results for third gene in the study\*\*\*

**OBX|**20|CWE|48018-6^**Gene(s) studied**^HGNC-Symb**|4.3|**2637^**CYP3A4**^HGNC-

Symb~2638^**CYP3A5**^HGNC-Symb|  
**OBX|**21|ST|47998-0^**Genotype display name**^LN**|4.3|\*1/\*1**~**\*1/\*1**|  
**OBX|**22|CWE|53040-2^**Genetic variation's effect on drug metabolism interp**^LN**|4.3|**LA25390-8^

**Rapid metabolizer**^LN|  
 \*\*\*Medication usage implications panel\*\*\*  
**OBX|**23|CWE|51963-7^**Medication assessed**^RxT-Ingrd**|4.3.1|**83367^**atorvastatin**^RxT-Ingrd|  
**OBX|**24|CWE|82116-5^**Medication usage suggestion [type]**^LN**|4.3.1|**LA26423-6^**Increase**

**Dose**^LN|  
**OBX|**25|TX|Pending LOINC 2^**Medication usage suggestion [narrative]**^LN**|4.3.1|Monitor for efficacy**.|

\*\*\* Results for fourth gene in the study\*\*\*  
**OBX|**26|CWE|48018-6^**Gene(s) studied**^HGNC-Symb**|4.4|**2625^**CYP2D**6^HGNC-Symb|  
**OBX|**27|ST|47998-0^**Genotype display name**^LN**|4.4|**\*1/\*1|  
**OBX|**28|CWE|53040-2^**Genetic variation's effect on drug metabolism interp**^LN**|4.4|**LA25391-

6^**Normal metabolizer**^LN|  
 \*\*\*Medication usage implications panel\*\*\*  
**OBX|**29|CWE|51963-7^**Medication assessed**^RxT-Ingrd**|4.4.1|**4493^**Fluoxetine**^RxT-Ingrd|  
**OBX|**30|CWE|82116-5^**Medication usage suggestion [type]**^LN**|4.4.1|**LA26425-1^**Normal**

**Response Expected**^LN|  
**OBX|**31|TX|Pending LOINC 2^**Medication usage suggestion [narrative]**^LN**|4.4.1|**Monitor for inhibition of

other drugs. Fluoxetine is a strong 2D6 inhibitor and is known to effect drugs which use the

CYP 2D6 pathway.|

\*\*\* Results for fifth gene in the study\*\*\*  
**OBX|**32|CWE|48018-6^**Gene(s) studied**^HGNC-SYmb**|4.5|**2621^**CYP2C1**9^HGNC-Symb|  
**OBX|**33|ST|47998-0^**Genotype display name**^LN**|4.5|**\***1/\*1**|  
**OBX|**34|CWE|53040-2^**Genetic variation's effect on drug metabolism interp**^LN**|4.5|**LA25391-6^

**Normal metabolizer**^LN|  
 \*\*\*Medication usage implications panel\*\*\*  
**OBX|**35|CWE|51963-7^Medication assessed^RxT-Ingrd**|4.5.1|**6754^**Meperidine**^RxT-Ingrd|  
**OBX|**36|CWE|82116-5^Medication usage suggestion [type]^LN**|4.5.1|**LA26425-1^**Normal Response**

**Expected**^LN|  
**OBX|**37|TX|Pending LOINC 2^**Medication usage suggestion [narrative]**^LN**|4.5.1|**Follow label dosing and

administration information. No change needed.|

## Complex Variant Example Messages

### Complex Variant – Example of non-pharmacogenomic complex variant haplotype

*Note(s):*

This is an example of a non-pharmocogenomic complex variant, which happens to be a haplotype.

The narrative text was invented based on a sample report on Gaucher’s disease, with the genetic details taken from NCBI’s ClinVar. It has a variant ID = 16895, and has the full HGVS expression of: 4297 NM\_001005741.2(GBA):c.[1448T>C;1483G>C;1497G>C] – Haplotype, which can be found at [http://www.ncbi.nlm.nih.gov/clinvar/variation/4297/](http://www.ncbi.nlm.nih.gov/clinvar/variation/4297/%20) .

**OBR**|1|Acme23469|Gen825750| 35693-1^GBA gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative^LN|R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*

**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient may have Gaucher's disease.|  
**OBX|**2|CWE|51967-8^**Genetic disease(s) assessed**^MedGen-Dis **|1|**C0017205^**Gaucher disease**^MedGen-Dis|

**OBX|**3|CWE|Pending LOINC 1^**Default transcript reference sequence**^RefSeq-T **|1|**

NM\_000157^ **NM\_000157**^RefSeq-T|

**OBX|**4|TX|81293-3^**Description of ranges of DNA sequences examined**^LN**|1|**Bi-directional sequence analysis

was performed to test for the presence of mutations in all coding regions and intron/exon boundaries of the GBA gene.|

**OBX|**5|CNE|48018-6^**Gene(s) assessed**^HGNC-Symb**|1.1|**4177^**GBA**^HGNC-Symb|

**OBX|**6|CNE|51968-6^**Discrete variation analysis overall interpretation**^LN|1|LA6576-8^**Positive**^LN|

**OBX|**7|TX|51969-4^**Full narrative report**^LN**|1|Result Summary**- Positive~~ **Result** – The following haplotype

heterozygous alteration was identified: Amino Acid changes: p.Ala495Pro, p.Val499=, p.Leu483Pro. DNA change: c.1483G>C (g.14481), c.1497G>C (g.14495), c.1448T>C (g.14446)~~ **Classification**: PATHOGENIC ~~ **Interpretation –** The haplotype 1483G>C (p.Ala495Pro), c.1497G>C (p.Val499=), c.1448T>C (p.Leu483Pro) alteration is a known pathogenic mutation. This result indicates that this individual is a carrier of Gaucher disease. This assumes that this individual is not clinically affected with Gaucher disease. While the clinical presentation associated with Gaucher disease can be variable, the p.Ala495Pro, p.Val499=, p.Leu483Pro haplotype mutation is associated with Gaucher's disease, type 1, Acute neuronopathic Gaucher's disease, Subacute neuronopathic Gaucher's disease, and Gaucher disease, perinatal lethal.~~ **Method** - Bi-directional sequence analysis was performed to test for the the presence of mutations in all coding regions and intron/exon boundaries of the GBA gene.

\*\*\* Technical details\*\*\*  
**OBX|**8|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029^GRCh37^LN|  
**OBX|**9|NM|82115-7^**dbSNP version**^LN**|1|147**|

\*\*\*Complex Variant: Report Section 5\*\*\*  
**OBX|**10|CWE|81260-2^**Complex variant ID**^ClinVar-V**|5.1|**

4297^**NM\_001005741.2(GBA):c.[1448T>C;1483G>C;1497G>C] – Haplotype**^ClinVar-V|  
**OBX|**11|CNE|81263-6^**Complex variant type**^LN|1.1|LA26218-0^Haplotype^LN|  
**OBX|**12|CWE|81259-4^**Associated phenotype**^MedGen-Dis|1.1|C0017205^Gaucher disease^MedGen-Dis|  
**OBX|**13|CNE|53037-8^**Clinical significance**^LN|1.1|LA6668-3^**Pathogenic**^LN|  
**OBX|**14|CNE|53034-5^**Allelic state**^LN|1.1|LA6706-1^**Heterozygous**^LN|

\*\*\*Attributes of First Simple Variant within the complex variant\*\*\*  
**OBX|**15|CNE|81252-9^**Simple variant**^ClinVar-V**|5.1.1|**

93450^**NM\_001005741.2(GBA):c.1483G>C (p.Ala495Pro)**^ClinVar-V|

\*\*\*Transcript Specification Variables\*\*\*  
**OBX|**16|CWE|48018-6^**Gene studied**^HGNC-Symb**|5.1.1|**4177^**GBA**^HGNC-Symb|  
**OBX|**17|CWE|51958-7^**Transcript RefSeq ID**^ RefSeq-T**|5.1.1|**NM\_001005741.2^**NM\_001005741.2**^RefSeq-T|  
**OBX|**18|CWE|41103-3^**DNA change c.HGVS**^ HGVS.c **|5.1.1|** c.1483G >C^**c.1483G>C**^HGVS.c|  
**OBX|**19|CWE|48005-3^**Amino acid change p.HGVS**^ HGVS.**|5.1.1|**p.Ala495Pro^**p.Ala495Pro**^HGVS.p|  
**OBX|**20|CWE|48019-4^**DNA change type**^LN**|5.1.1|** LA6690-7^**Substitution**^LN |  
**OBX|**21|CWE|48006-1^**Amino acid change type**^LN**|5.1.1|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**22|CWE|48013-7^**Genomic reference sequence**^ RefSeq-G **|5.1.1|**

NC\_000001.10^**NC\_000001.10**^RefSeq-G|  
**OBX|**23|ST|69547-8^**Genomic ref allele**^LN**|5.1.1|C**|  
**OBX|**24|NR|81254-5^**Genomic allele start-end**^LN**|5.1.1|155205008**^**155205008**|  
**OBX|**25|ST|69551-0^**Genomic alt allele**^LN**|5.1.1|G**|  
 \*\*\*Other variables\*\*\*  
**OBX|**26|CNE|81255-2^**dbSNP ID**^dbSNP**|5.1.1|**rs368060^**rs368060**^dbSNP|  
**OBX|**27|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|5.1.1|**1q22^**1q22**^Chrom-Loc|  
**OBX|**28|CNE|48002-0^**Genomic source class**^LN**|5.1.1|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*

**OBX|**29|CNE|53037-8^**Clinical significance**^LN**|5.1.1|**LA6675-8^**Benign**^LN|

\*\*\*Allelic state/phase information\*\*\*

**OBX|**30|CWE|82120-7^**Allelic phase [Type]**^LN**|5.1.1|**LA6112-2^

**1st set of variants in CIS relation to each other**^LN|  
**OBX|**31|CNE|82309-6^**Basis for allelic phase**^LN**|5.1.1|**LA26426-9^**Directly measured**^LN|

\*\*\*Attributes of Second Simple Variant within the complex variant\*\*\*  
**OBX|**32|CNE|81252-9^**Simple variant**^ClinVar-V**|5.1.2|**

93451^**NM\_001005741.2(GBA):c.1497G>C (p.Val499=)**^ClinVar-V|

\*\*\*Transcript Specification Variables\*\*\*  
**OBX|**33|CWE|48018-6^**Gene studied**^HGNC-Symb**|5.1.2|**4177^**GBA**^HGNC-Symb|  
**OBX|**34|CWE|51958-7^**Transcript RefSeq ID**^RefSeq-T**|5.1.2|**NM\_001005741.2^**NM\_001005741.2**^RefSeq-T|  
**OBX|**35|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|5.1.2|**c.1497G>C^**c.1497G>C**^HGVS.c|  
**OBX|**36|CWE|48005-3^**Amino acid change p.HGVS**^ HGVS.p**|5.1.2|**p.Val499=^**p.Val499=**^HGVS.p|  
**OBX|**37|CWE|48019-4^**DNA change type**^LN**|5.1.2|**LA6690-7^**Substitution**^LN |

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**38|CWE|48013-7^**Genomic reference sequence**^RefSeq-G **|5.1.2|**NC\_000001.10^**NC\_000001.10**^RefSeq-G|  
**OBX|**39|ST|69547-8^**Genomic ref allele**^LN**|5.1.2|C**|  
**OBX|**40|NR|81254-5^**Genomic allele start-end**^LN**|5.1.2|155204994**^**155204994**|  
**OBX|**41|ST|69551-0^**Genomic alt allele**^LN**|5.1.2|G**|  
 \*\*\*Other variables\*\*\*  
**OBX|**42|CNE|81255-2^**dbSNP ID**^dbSNP**|5.1.2|** rs1135675^**rs1135675**^dbSNP|  
**OBX|**43|CWE|48001-2^**Cytogenetic location of variant**^LN**|5.1.2|**1q22^**1q22**^Chrom-Loc|  
**OBX|**44|CNE|48002-0^**Genomic source class**^LN**|5.1.2|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**45|CNE|53037-8^**Clinical significance**^LN**|5.1.2|**LA6675-8^**Benign**^LN|  
 \*\*\*Allelic state/phase information\*\*\*

**OBX|**46|CWE|82120-7^**Allelic phase [Type]**^LN**|5.1.1|**LA6112-2^

**1st set of variants in CIS relation to each other**^LN  
**OBX|**47|CNE|82309-6^**Basis for allelic phase**^LN**|5.1.1|**LA26426-9^**Directly measured**^LN|

\*\*\*Attributes of Third Simple Variant within the complex variant\*\*\*  
**OBX|**48|CNE|81252-9^**Simple variant**^ClinVar-V**|5.1.3|**

4288^**NM\_000157.3(GBA):c.1448T>C (p.Leu483Pro)**^ClinVar-V|

\*\*\*Transcript Specification Variables\*\*\*  
**OBX|**49|CWE|48018-6^**Gene studied**^HGNC-Symb**|5.1.3|**4177^**GBA**^HGNC-Symb|  
**OBX|**50|CWE|51958-7^**Transcript RefSeq ID**^ RefSeq-T **|5.1.3|**NM\_000157.3^**NM\_000157.3**^RefSeq-T|  
**OBX|**51|CWE|41103-3^**DNA change c.HGVS**^HGVS.c**|5.1.3|**c.1448T>C^**c.1448T>C**^HGVS.c|  
**OBX|**52|CWE|48005-3^**Amino acid change p.HGVS**^ **HGVS.p|5.1.3|**p.Leu483Pro^**p.Leu483Pro**^HGVS.p|  
**OBX|**53|CWE|48019-4^**DNA change type**^LN**|5.1.3|**LA6690-7^**Substitution**^LN|  
**OBX|**54|CWE|48006-1^**Amino acid change type**^LN**|5.1.3|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**55|CWE|48013-7^**Genomic reference sequence**^ RefSeq-G**|5.1.3|**NC\_000001.10^**NC\_000001.10**^RefSeq-G|  
**OBX|**56|ST|69547-8^**Genomic ref allele**^LN**|5.1.3|A**|  
**OBX|**57|NR|81254-5^**Genomic allele location**^LN**|5.1.3|155205043**^**155205043**|  
**OBX|**58|ST|69551-0^**Genomic alt allele**^LN**|5.1.3|G**|  
 \*\*\*Other variables\*\*\*  
**OBX|**59|CNE|81255-2^**dbSNP ID**^dbSNP**|5.1.3|** rs421016^**rs421016**^dbSNP|  
**OBX|**60|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|5.1.3|**1q22^**1q22**^Chrom-Loc|  
**OBX|**61|CNE|48002-0^**Genomic source class**^LN**|5.1.3|**LA6683-2^**Germline**^LN|  
 \*\*\*Interpretations\*\*\*  
**OBX|**62|CNE|53037-8^**Clinical significance**^LN**|5.1.3|**LA6668-3^**Pathogenic**^LN|  
**OBX|**63|CWE|81259-4^**Probable associated phenotype**^LN**|5.1.3|**C0017205^**Gaucher disease**^MedGen-Dis|  
 \*\*\*Allelic state/phase information\*\*\*

**OBX|**64|CWE|82120-7^**Allelic phase [Type]**^LN**|5.1.1|**LA6112-2^

**1st set of variants in CIS relation to each other**^LN  
**OBX|**65|CNE|82309-6^**Basis for allelic phase**^LN**|5.1.1|**LA26426-9^**Directly measured**^LN|

### Complex Variant, Example of pharmacogenomics study that details results for each allele

*Note(s):*

This is an example of a pharmocogenomic complex variant, which happens to be a haplotype. We couldn’t find the genetic details of the variants that underlay the pharmacogenomics example, so we did not have haplotype example to tie to it. This is stand-alone Haplotype to show how a complex variant would be constructed. It came from NCBI with variant ID =16895, and has the full HGVS expression of: 16895 (NM\_000106.5(CYP2D6):c.[886C>T;457G>C] – Haplotype), which can be found at <http://www.ncbi.nlm.nih.gov/clinvar/variation/16895/> .

Note that in this complex variant example, we have temporarily used the allele ID for the LOINC 81252-9 “Simple Variant” field for the simple variants inside the complex variant, rather than variant ID because some alleles submitted with a complex variant as one package do not yet have variant IDs. They will shortly, but not in time for this release of the guide.

**OBR**|1|Acme23469|Gen825750|47403-1^ CYP2D6 gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative^LN |R|201608030830| 201608091650|

\*\*\*Variables that Apply to Overall Study: Report Section 1\*\*\*

**OBX|**1|TX|53577-3^**Reason for study**^LN**|1|**Patient drug not responding.|  
**OBX|**2|CWE|Pending LOINC 1^**Default transcript reference sequence**^RefSeq-T**|1|**

NM\_000106.5^**NM\_000106.5**^RefSeq-T

**OBX|**3|CNE|48018-6^**Gene(s) assessed**^HGNC-Symb **|1.1|**2625^**CYP2D6**^HGNC-Symb|

**OBX|**4|CWE|36908-2^**Gene mutations tested**^LN**|1.1|**16895^**[NM\_000106.5(CYP2D6):c.886C>T**

**(p.Arg296Cys)][NM\_000106.5(CYP2D6):c.1457G>C (p.Ser486Thr)]**^ClinVar-V|

**OBX|**5|CNE|51968-6^**Discrete variation analysis overall interpretation**^LN|1|LA6576-8^**Positive**^LN|

\*\*\* Technical details\*\*\*

**OBX|**6|CWE|62374-4^**Human reference sequence assembly**^LN**|1|**LA14029-6^**GRCh37**^LN|

**OBX|**7|NM|82115-7^**dbSNP version**^LN**|1|147**|

\*\*\*Complex Variant: Report Section 5\*\*\*  
**OBX|**8|CWE|81260-2^**Complex variant**^ClinVar-V**|5.1|**

16895^**NM\_000106.5(CYP2D6):c.[886C>T;457G>C] – Haplotype**^ClinVar-V|  
**OBX|**9|ST|81262-8^**Complex variant HGVS name**^HGVS.c**|5.1|c.[886C>T;457G>C]**^^HGVS.c|  
**OBX|**10|CNE|81263-6^**Complex variant type**^LN**|5.1|**LA26218-0^**Haplotype**^LN|  
**OBX|**11|CWE|81259-4^**Associated phenotype**^LN**|5.1|**C1837157^**Debrisoquine, ultrarapid**

**metabolism o**f^MedGen-Dis|  
**OBX|**12|CNE|53034-5^**Allelic state**^LN**|5.1|**LA6706-1^**Heterozygous**^LN|

\*\*\*Attributes of First Simple Variant within the complex variant\*\*\*  
**OBX|**13|CNE**|**81252-9^**Simple variant**^ClinVar-V**|5.1.1|**

**31934^NM\_000106.5(CYP2D6):c.886C>T (p.Arg296Cys)**^ClinVar-V|

\*\*\*Transcript Specification Variables\*\*\*  
**OBX|**14|CWE|48018-6^**Gene studied**^LN**|5.1.1|** 2625^**CYP2D6**^HGNC-Symb|  
**OBX|**15|CWE|51958-7^**Transcript RefSeq ID**^LN**|5.1.1|**NM\_000106.5^**NM\_000106.5**^RefSeq-T|  
**OBX|**16|CWE|41103-3^**DNA change c.HGVS**^LN**|5.1.1|**c.886C>T^**c.886C>T**^HGVS.c|  
**OBX|**17|CWE|48005-3^**Amino acid change p.HGVS**^LN**|5.1.1|**p.Arg296Cys^**p.Arg296Cys**^HGVS.p|  
**OBX|**18|CWE|48019-4^**DNA change type**^LN**|5.1.1|**LA6690-7^**Substitution**^LN|  
**OBX|**19|CWE|48006-1^**Amino acid change type**^LN**|5.1.1|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**20|CWE|48013-7^**Genomic reference sequence**^LN**|5.1.1|**

NC\_000022.10^**NC\_000022.10**^RefSeq-G|  
**OBX|**21|ST|69547-8^**Genomic ref allele**^LN**|5.1.1|A**|  
**OBX|**22|NR|81254-5^**Genomic allele start-end**^LN**|5.1.1|42523943^42523943**|  
**OBX|**23|ST|69551-0^**Genomic alt allele**^LN**|5.1.1|A**|  
 \*\*\*Other variables\*\*\*  
**OBX|**24|CNE|81255-2^**dbSNP ID**^dbSNP**|5.1.1|**rs16947^**rs16947**^dbSNP|  
**OBX|**25|CWE|48001-2^**Cytogenetic location of variant**^Chrom-Loc**|5.1.1|**22q13.2^**22q13.2**^Chrom-Loc|  
**OBX|**26|CNE|48002-0^**Genomic source class**^LN**|5.1.1|**LA6683-2^**Germline**^LN|

\*\*\*Interpretations\*\*\*  
**OBX|**27|CNE|69548-6^**Genomic variant assessment**^LN**|5.1.1|**LA9633-4^**Present**^LN|

\*\*\*Attributes of Second Simple Genetic Variant\*\*\*  
**OBX|**28|CNE|81252-9^**Simple variant**^ClinVar-V**|5.1.2|**

**38485^NM\_000106.5(CYP2D6):c.1457G>C (p.Ser486Thr)**^ClinVar-V|

\*\*\*Transcript Specification Variables\*\*\*  
**OBX|**29|CWE|48018-6^**Gene studied**^LN**|5.1.2|**38485^**CYP2D6**^HGNC-Symb|  
**OBX|**30|CWE**|**51958-7^**Transcript RefSeq ID**^RefSeq-T**|5.1.2|**

NM\_000106.5^**NM\_000106.5**^RefSeq-T|  
**OBX|**31|CWE**|**41103-3^**DNA change c.HGVS**^LN**|5.1.2|**c.1457G>C^**c.1457G>C**^HGVS.c|  
**OBX|**32|CWE**|**48005-3^**Amino acid change p.HGVS**^LN**|5.1.2|**p.Ser486Thr^**p.Ser486Thr**^HGVS.p|  
**OBX|**33|CWE|48019-4^**DNA change type**^LN**|5.1.2|**LA6690-7^**Substitution**^LN|  
**OBX|**34|CWE|48006-1^**Amino acid change type**^LN**|5.1.2|**LA6698-0^**Missense**^LN|

\*\*\*Genomic specification variables (VCF-like representation)\*\*\*  
**OBX|**35|CWE|48013-7^Genomic reference sequence^LN**|5.1.2|**

NC\_000022.10**^NC\_000022.10**^RefSeq-G|  
**OBX|**36|ST|69547-8^**Genomic ref allele**^LN**|5.1.2|G**|  
**OBX|**37|NR|81254-5^**Genomic allele start-end**^LN**|5.1.2|42522613^42522613**|  
**OBX|**38|ST**|**69551-0^**Genomic alt allele**^LN**|5.1.2|G**|  
 \*\*\*Other variables\*\*\*  
**OBX|**39|CNE|81255-2^**dbSNP ID**^dbSNP**|5.1.2|** rs1135840^**rs1135840**^dbSNP|  
**OBX|**40|CWE|48001-2^**Cytogenetic location of variant**^LN**|5.1.2|**22q13.2^**22q13.2**^Chrom-Loc|  
**OBX|**41|CNE|48002-0^**Genomic source class**^LN**|5.1.2|**LA6683-2^**Germline**^LN|

\*\*\*Interpretations\*\*\*  
**OBX|**42|CNE|69548-6^**Genomic variant assessment**^LN**|5.1.2|**LA9633-4^**Present**^LN|

1. Ye Wang Y, Lynch P, Kanduru A, Hook J, Mericle L, Ludet C, Vreeman DJ, Clement J. McDonald CJ. LHC-Forms and Related Widgets for Capturing and Tuning Health Data. AMIA Annu Symp Proc. 2016 (Accepted). [↑](#footnote-ref-2)