Development of LOINC for Integrating Constitutional Cytogenetic Test Result Reports into Electronic Health Records

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Abstract

Objective: To develop *Logical Observation Identifiers Names and Codes* (LOINC) codes to represent constitutional cytogenetic test results for electronically exchanging coded and structured result reports. The LOINC codes developed must be flexible and sustainable for easy maintenance. The goal is to create a standard set of codes that are flexible enough to be used for all unique conventional and molecular cytogenetic results. **Design:** Patient de-identified sample result reports were obtained from ARUP Laboratories for a variety of normal and abnormal constitutional studies using G-banding, FISH and array-CGH. Information models were created to capture the semantic relationships of the key data elements that existed in the reports. Sample reports were subsequently obtained from Emory and Mayo Clinic Cytogenetics Laboratories to verify the information models. The information models were then used to guide the systematic creation of the LOINC codes. **Results:** A post-coordinated approach was used in developing the LOINC codes for cytogenetics test results. LOINC panel codes were created to represent the hierarchical structures implied by the reports. A master panel was created to contain three LOINC subpanels; each of the three subpanels held the structure for chromosome analysis results that uses a different technique. **Conclusion:** The LOINC codes we created met our objective and will allow the use of well established health informatics standards to exchange coded and structured cytogenetic test results between testing laboratories and ordering institutions. Use of standard structures and terminologies for cytogenetic results is critical for effective communication between testing laboratories and clinicians. This minimizes misinterpretation, leads to consistency, and provides the EHR systems flexibility of customizing formatting to present more clinician-friendly reports.

Keywords

cytogenetics, LOINC, information model

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1 Introduction

Discoveries in genetics and genomics research are increasing at a rapid rate. The number of clinically available genetic tests has also increased dramatically during the past decade [1, 2]. From primary care to specialty care settings, genetic testing is changing many aspects of clinical practice and patient services. Integration of genetic and genomic data with traditional clinical data to support the diagnostic and treatment decisions at the point of care for the individual patient is touted as ushering in a new era of personalized medicine [3, 4, 5].

Realization of the promise of personalized medicine depends on effective communication between laboratories and clinical settings. The laboratory result report plays a vital role in this communication channel. However, the format of genetic test requisitions and result reports vary from laboratory to laboratory; test results lack clarity about the clinical significance of the findings and are not clinician friendly [6]. All these factors have affected efficient communication between testing laboratories and clinicians. The problem has been further compounded by clinical providers' lack of basic knowledge about genetics, and their lack of confidence in interpreting genetic results [7, 8]. This could lead to potential misinterpretation of test results and compromised patient care; genetic test result reports that use standardized terminology and improved formatting are critical to address these problems.

Realization of the benefits provided by genetic and genomic advances in clinical care depends on effective access to the right information at the right time. Electronic Health Records (EHRs) promise to improve patient care, especially by providing advanced Clinical Decision Support (CDS) at the point of care. Incorporating genetic test results into the patient's EHR is a major step forward to take full advantage of genetic/genomic advances in clinical practice. However, EHRs today require significant modifications in order to consume genetic/genomic information and to effectively utilize such information in making clinical decisions [9, 10].

Standard terminologies that are tightly coupled with standard information models are the foundations of developing CDS-enabled EHRs. However, current standard terminologies for genetic test results are not sufficient. As the movement toward predictive, personalized, preventive medicine accelerates, we must develop terminology infrastructure before clinical information systems will be able to handle the high volumes of genetic and genomic data expected in the near future.

We previously evaluated the Logical Observation Identifiers Names and Codes (LOINC) system for representing cytogenetic test names and their results [11]. LOINC is the most widely adopted standard for laboratory test result names in the United States and internationally [12]. We found that current LOINC content is not sufficient to encode cytogenetic test names and test results. In this article, we describe how new LOINC codes for constitutional cytogenetic test results were developed. As the demand for standard terminologies representing genetics and genomics data continues to increase, the approach we took and the experiences we gained through this development process may be especially useful for others to use when developing standard terminologies to support the integration of genetic and genomic data into EHRs. Others may also find our approach useful for developing standard terminologies in general.

2 Background

2.1 Cytogenetic Test

Cytogenetic tests evaluate chromosomes from the nucleus of the cell for changes in number or structure. Cytogenetic testing is used in various clinical situations. These historically included assessment of a developmentally delayed child, evaluation of a cancerous tumor, or prenatal studies to detect chromosomal anomalies in a fetus [13]. A constitutional cytogenetic abnormality is one which occurs in the germline. A cancerous cytogenetic abnormality is an acquired (somatic) genetic change associated with a neoplastic process.

The emerging field of cytogenomics includes conventional cytogenetics, which uses chromosomal banding techniques such as G-banding, in addition to molecular technologies, such as fluorescence in situ hybridization (FISH), and cytogenomic microarray (arr). FISH is often used in prenatal diagnosis when results are needed rapidly to detect chromosomal aneusomies such as Down syndrome (trisomy 21), and also to detect chromosomal deletions, duplications, or rearrangements that are not visible using microscopy.[14]. Cytogenomic microarray (arr) circumvents a limitation of FISH as it does not require foreknowledge of the chromosomal loci being evaluated.

The introduction of arr to clinical cytogenetics has facilitated the genome wide detection of DNA copy number imbalances at resolutions significantly higher than previously attainable [14]. Arr analysis allows for the simultaneous analysis of hundreds or thousands of discrete loci, not possible within a single FISH experiment and at a much higher resolution than conventional cytogenetic analysis. Although current arr technologies cannot identify balanced rearrangements, most chromosome analyses that are performed on individuals with phenotypic abnormalities, developmental delays, or intellectual disability are performed to detect unbalanced chromosomal rearrangements, (gains and losses of chromosomal segments) and have been proposed to be a first tier test [15].

Traditional cytogenetics methods can detect gross chromosomal lesions. G-banded karyotyping is generally limited to the detection of genomic imbalances in the 5-10 Mb range. Most FISH assays used in a clinical cytogenetic setting detect submicroscopic changes no smaller than 50 kb, and only in limited targeted areas. In contrast, available oligonucleotide platforms can now detect genomic imbalances as small as 500 bp [16], and the International

Standard Cytogenomic Array Consortium (ISCA) currently recommends a resolution of >=400 kb throughout the genome as a balance of analytical and clinical sensitivity to detect copy number variants [15].

The International System for Human Cytogenetic Nomenclature (ISCN) is critical in reporting cytogenetic test results. ISCN was created by the International Standing Committee on Human Cytogenetic Nomenclature to represent the outcome of cytogenetic tests [17]. The latest version of ISCN was published in 2009. ISCN has been the gold standard of describing chromosome aberrations for almost 40 years. The College of American Pathologists (CAP) checklist and the American College of Medical Genetics (ACMG) guidelines for cytogenetics indicate that current ISCN must be used in clinical reports [18, 19].

2.2 Cytogenetic Test Results from ARUP to Intermountain Healthcare

Intermountain Healthcare is a nonprofit integrated health care delivery system consisting of 22 hospitals, and more than 130 outpatient clinics. Cytogenetic tests ordered by Intermountain physicians are performed by the ARUP Laboratories. ARUP is a national clinical and anatomic pathology reference laboratory owned by the University of Utah [20].

Cytogenetic test results are transmitted electronically from ARUP Laboratories to Intermountain Healthcare through Health Level Seven (HL7) version 2.x messages. HL7 version 2.x standards are the most widely implemented standards for healthcare data exchange in the world. HL7 version 2.x defines a series of electronic messages to support administrative, logistical, financial as well as clinical processes [21]. Each HL7 version 2.x message is composed of a number of segments. Each segment begins with a three-character literal value that identifies it within a message. For example, NTE represents a Notes and Comments segment, which is used to transmit free text notes and comments; OBX represents an Observation/Result segment, which is used to transmit a single observation or observation fragment. A segment contains a group of logically combined data fields. HL7 v2.x mostly uses a textual, non-XML encoding syntax based on delimiters, such as "|" and "^".

After the cytogenetic test results are received electronically by Intermountain Healthcare, they are stored in Intermountain's Clinical Data Repository (CDR) [22]. However, the results are not sent in a coded and structured format. The report is contained in an HL7 NTE segment as a text blob, and is stored as narrative text in the CDR. The test codes that are sent in the OBX-3 segment are local codes; they are not mapped to LOINC. One reason for this is that there are very few LOINC codes available for coding cytogenetic tests and results. A second reason is that the existing LOINC codes are not consistent with how the ARUP cytogenetic tests are named or with how the results are represented in actual reports [11]. For example, no LOINC code is available for representing the cytogenetic test results that are expressed in ISCN.

2.3 HL7 Standard for Reporting Genetic Test Results

HL7 approved a new implementation guide for electronic exchange of results of genetic variation tests called the "HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-qualified Genetic Variation Model, Release 1" in 2009 [23]. This guideline was sponsored by the Clinical Genomics Work Group. The Genetic Variation Model contains a set of four nested LOINC panels; the parent panel is Genetic Analysis Master Panel, which has exactly one Genetic Analysis Summary Panel, and zero-to-one Genetic Analysis Discrete Result Panel. The Genetic Analysis Discrete Result Panel has zero-to-many DNA Analysis Discrete Sequence Variation Panel.

Intermountain Healthcare and Partners Healthcare Center for Personalized Genetic Medicine have developed a pilot implementation of the guideline. The two organizations recently announced the first transmission of a coded and structured genetic test result sent electronically through the interface established between the two institutions, with the result being stored as part of the patient's EHR [24].

However, this HL7 standard and the implementation effort are focused on reporting genetic test results performed using sequencing or genotyping technology for the identification of DNA sequence variations contained within a gene [23]. To our knowledge, no similar work has been done or is ongoing for exchange of cytogenetic test results. The development effort that we describe in this article aims to fill the gap in existing standards for cytogenetic test result reporting.

3 Formulation process

After receiving IRB approval, we obtained patient de-identified sample result reports for constitutional cytogenetics analyses from ARUP Laboratories. The sample result reports were chosen so they would cover tests that were performed using different types of cytogenetic techniques including G-banding, FISH, and arr. The sample reports also represented a variety of results, including normal, abnormal, and "findings of unknown clinical significance". We also obtained test names from the ARUP online test menu. We analyzed the sample result reports and extracted a list of key data elements that existed in the reports. Before we made any new LOINC terms, we first created information models that capture the semantic relationships of these data elements. The information models were then used to guide the systematic creation of the LOINC codes.

To ensure that the information models and the LOINC codes that would be developed could be generalized to other institutions besides ARUP, we contacted two other

large cytogenetics laboratories in the country to request the same variety of sample patient de-identified test names and result reports from them. We received sample reports from the Mayo Clinic Cytogenetics Laboratory (Mayo) as well as the Emory Cytogenetics Laboratory (Emory). The sample result reports for each laboratory were analyzed, and their key data elements were also extracted. We evaluated the new data elements and new relationships that were identified in the Mayo and Emory reports, which did not exist in the ARUP reports, and analyzed whether the information model required modification to accommodate the new data elements.

After we had established the information models for cytogenetic test results based on reports from these three cytogenetics laboratories, we compared the cytogenetics model with the HL7 V2 Genetic Variation model. The goal was to reuse the common structure and the existing LOINC codes that are defined in the Genetic Variation model as much as possible.

In the end, we created proposed LOINC codes for unique data elements that were contained in the cytogenetics models. Following the same strategy that was used to develop the HL7 V2 Genetic Variation Model, LOINC panel codes were created to represent the hierarchical structures implied by the reports. To avoid proposing creation of duplicate codes in the LOINC database, the LOINC database was searched thoroughly beforehand, and any potential matching codes were analyzed to see whether they fit our needs and should be reused. The LOINC codes have been accepted by the LOINC Committee and are included in version 2.34 of the LOINC data base that was released in December 2010.

4 Model description

We created three information models based on the sample clinical reports from ARUP, Mayo, and Emory cytogenetics laboratories. Figures 1 to 3 show the information models for conventional chromosome studies using G-banding, FISH studies, and arr studies respectively. The information models contain data elements such as chromosome analysis result and chromosome analysis overall interpretation. We did not include the specimen type as an attribute in the information models, since specimen is represented by one of the six LOINC axes and the LOINC code is carried in HL7's observation identifier. We have also excluded standard data elements, such as patient date of birth, administrative sex, and specimen collection date, which are a routine part of laboratory reporting, and are carried by dedicated fields in segments that are a routine part of an HL7 observation message, rather than as separate OBX segments identified with specialized LOINC codes. Because ISCN descriptors can change over time, accurate interpretation of cytopathology reports requires knowledge of the ISCN version number used to generate the report. We have not had to include the ISCN version number in our information model for cytogenetics reports because the version of a code system is part of the internal structure of the HL7 "coded with exception" (CWE) data type. Because of the changes in the ISCN coding system over time, the receiving EHR system will also have to keep the ISCN version number with cytogenetics test results it stores in the CDR.

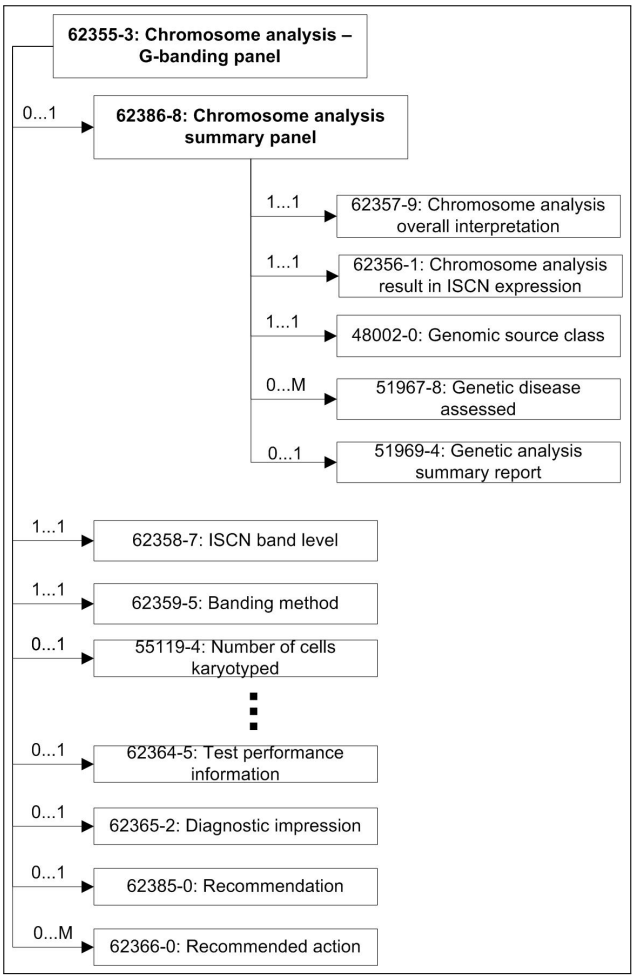


Figure 1: Chromosome analysis G-banding panel.

We created a set of nested LOINC panel codes that define the hierarchical structure of the results. The overall parent is, "Chromosome analysis master panel in Blood or Tissue" (LOINC # 62389-2). It contains three panels which define, respectively, the results of a G-Band, FISH and arr study: "Chromosome analysis panel in Blood or Tissue by Banding" (LOINC # 62355-3), "Chromosome analysis panel in Blood or Tissue by Fluorescence in situ hybridization" (FISH) (LOINC # 62367-8) and "Chromosome analysis microarray copy number change panel in Blood or Tissue by arrCGH" (arr) (LOINC # 62343-9). The LOINC terms within the each panel carry data types, cardinalities and descriptions. For LOINC terms that have categorical values, we also created pre-defined answer lists. As shown in Figure 4, the chromosome analysis master panel contains at least one of the G-banding, FISH, or arr copy number change panel, and a required chromosome analysis summary panel. The master panel allows the laboratory to report results of individual G-

banding, FISH, or arr copy number change test results alone, or as two or more of the three tests combined.

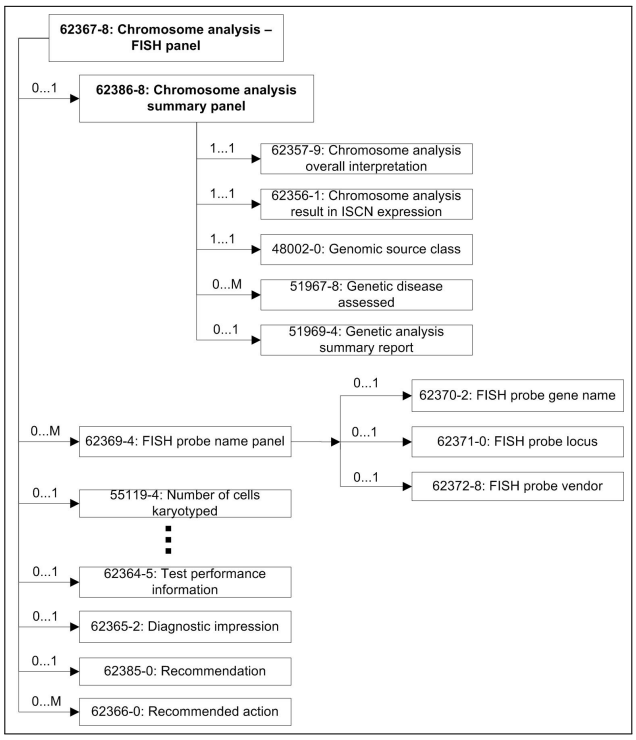


Figure 2: Chromosome analysis FISH panel.

The chromosome analysis summary panel must contain one chromosome analysis overall interpretation, which is the overall interpretation of the test. A LOINC answer list, whose values can be "normal", "abnormal", or "clinical significance unknown", is provided with this code. The master panel contains one genomic source class, whose LOINC code has an answer list with coded values such as "germline", "somatic", and "prenatal". The summary panel may have zero to many genetic disease assessed elements, and an optional genetic analysis summary report element. The summary report permits the lab to send a traditional narrative report embedded in the message. The chromosome analysis summary panel beneath the master panel will always report the overall summary of the test results. If only one method (G-banding, FISH, or arr) is used during the chromosome analysis, the optional chromosome analysis summary panel that is contained under each G-banding, FISH, or arr copy number change panel should not be used. For a given test, if multiple methods are applied, then the chromosome analysis summary panel at the higher level would allow an overall summary to be presented, and the chromosome analysis summary panel at the lower levels of each multiple method will allow summary at individual levels to be reported. The summary panel must also contain a chromosome analysis result in ISCN expression; i.e., a cytogenetics test result defined in the ISCN syntax - which provides precise, unambiguous descriptions of the cytogenetic findings. For example: "46,XX", which indicates a normal female; and "47,XY,+21", which indicates a male with trisomy 21 (an extra copy of chromosome 21, commonly known as Down syndrome). These are the two simplest examples; the ISCN notation for arr copy number change and FISH results can be quite lengthy and include precise breakpoint designations at the detailed level of individual base-pairs. For example, "arr 20q13.2q13.33(51,001,876-62,375,085)x1,22q13.33(48,533,211-49,525,263)x3" is an ISCN notation for a microarray analysis that shows a single copy loss on 20q and a single copy gain on 22q [17].

In addition to the summary panel, G-banding, FISH, and arr copy number change panels include discrete information that is specific to the technique. For example, it is important to report the human reference sequence assembly release number for an arr analysis. This indicates which version of the human assembly was used for the analysis.

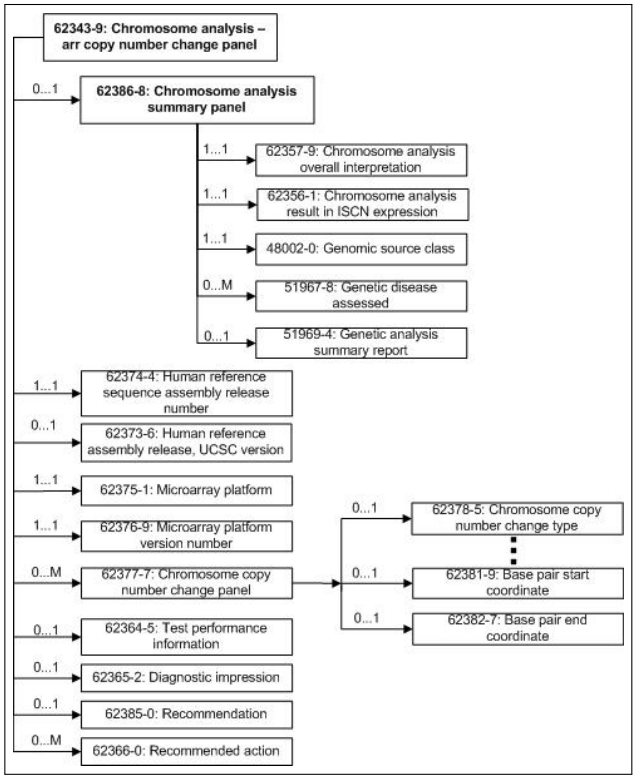


Figure 3: Chromosome analysis arr copy number change panel.

5 Validation through example

We formed HL7 version 2.5.1 standard messages based on the LOINC codes that we developed to represent the content of sample cytogenetic reports from three laboratories: ARUP, Emory, and Mayo. Figure 5 shows the HL7 version 2.5.1 representation of the G-banding chromosome analysis report presented in Figure 6. Figure 7 shows the HL7 v2.5.1 message for the arr report of copy number changes presented in Figure 8.

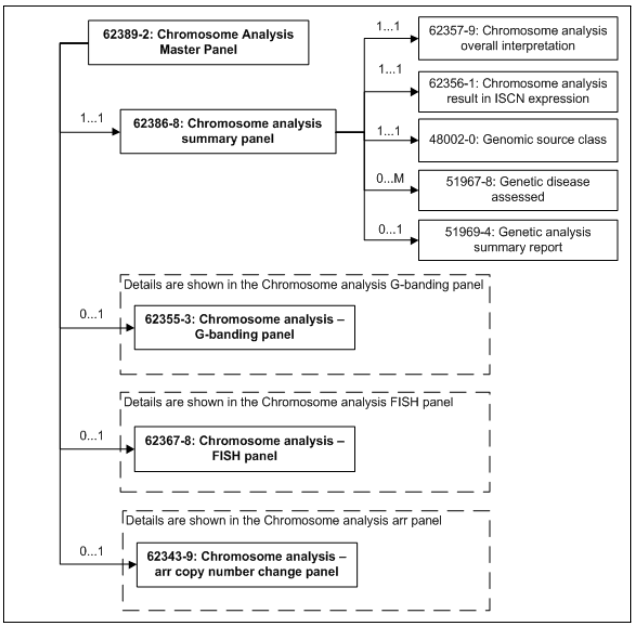


Figure 4: Chromosome analysis master panel.

OBR|1||PO-1000^ARUP|200291^Chromosome analysis chorionic villus sampling^99ARU-ORDER-TEST-ID||20100702000000|20100702100909|||||201070201410||12345^Dr.Jones||||| 20080703000000|||F|||||^Fetal demise|||||||||||||| 62389-2^Chromosome analysis master panel^LN

SPM|1|||^Placental tissue - Villi||||||||||20100702100909

OBR|2||PO-1000-1^ARUP|62355-3^Chromosome analysis G-banding^LN||20100702000000 |20100702100909|||||201070201410||12345^Dr.Jones |||||201070201410|||F||||PO-1000^ARUP

OBX|1|CWE|62358-7^ISCN band level^LN||LA14112-9^425^LN|||||F |201070201410|||||||||ARUP Laboratories

OBX|2|CWE|62359-5^Banding method^LN||LA14013-9^G-banding^LN|||||F |20080702100909|||||| ||||ARUP Laboratories

OBX|3|NM|62361-1^Numer of cells counted^LN||20|||||F|201070201410 |||||||||ARUP Laboratories

OBX|4|CWE|62366-0^Recommended action^LN||LA14020-4^Genetic counseling recommended^LN| |||||F|201070201410|||||||||ARUP Laboratories

OBX|5|FT|62385-0^Recommendation^LN||1. Genetic counseling. 2. Monitor subsequent pregnancies with prenatal diagnosis|||||F|201070201410|||||||||ARUP Laboratories

(... more OBXs could be placed here to represent other information in the G-banding panel...)

OBR|3||PO-1000-2^ARUP|62386-8^Chromosome analysis summary panel^LN||20100702000000 |20100702100909|||||201070201410||12345^Dr.Jones |||||201070201410|||F||||PO-1000^ARUP

OBX|1|CWE|62357-9^Chromosome analysis result overall interpretation^LN||LA12748-2^Abnormal^LN|||||F|201070201410|||||||ARUP Laboratories

OBX|2|CWE|62356-1^Chromosome analysis result in ISCN expression^LN||47,XY^^2.16.840.1.113883.6.299^^^^2005|||||M|201070201410|||||||ARUP Laboratories

OBX|3|CWE|48002-0^Genomic source class^LN||LA6683-3^Prenatal^LN|||||F| 201070201410 |||||||||ARUP Laboratories

(... more OBXs could be placed here to represent other information in the summary panel...)

Figure 5: Sample HL7 version 2 message for chromosome analysis G-banded test result.

In a message, nested Observation Request (OBR) segments are used to reflect the LOINC panel structures. OBRs are nested via links expressed in OBR-29-parent field, the same technique used in the HL7 implementation guide for genetic variation results [23]. The LOINC codes contained in a panel correspond to the Observation (OBX) segments. Each new panel of observations begins with an OBR segment that carries the LOINC code for that panel and is followed by a series of OBX's, each of which carries the LOINC code (OBX-3 field), and the value (OBX-5 field). For example, to represent the overall interpretation that the arr chromosome analysis test is abnormal: OBX-3 holds the LOINC code for "chromosome analysis overall interpretation"; the concept for "Abnormal" is placed in OBX-5 as the value.

We picked 20 cytogenetics reports across a wide spectrum including FISH, G-banding, and arr to verify that the proposed HL7 version 2 message had a place for expressing all of the most important information in these reports. We dissected these result reports based on the LOINC panels and codes. By dissecting these reports, we were able to represent all of the key data elements contained in the result reports in coded and structured format using the information models and the LOINC codes that we developed.

Specimen received

Specimen type: Placental Tissue- Villi
Reason for referral: Fetal Demise
Test performed: Chromosome Analysis

Laboratory analysis

Number of cells counted: 20
Number of colonies counted: N/A
Number of cells analyzed: 10
Number of cells karyotyped: 10
ISCN Band level: 425
Banding Method: G-Banding

Chromosome results: 47,XY,+21

Diagnostic Impression:
Metaphase cells analyzed revealed a male chromosome complement with an additional chromosome 21 seen in each metaphase. These results are consistent with the diagnosis of Down Syndrome.

Recommendation:
1. Genetic counseling.
2. Monitor subsequent pregnancies with prenatal diagnosis.

Figure 6: Partial sample report of chromosome analysis G-banding.

6 Discussion

The Secretary of the Department of Health and Human Services stated at the American Health Information Community (AHIC) meeting on September 12, 2006, "...genomics will play an increasingly larger role in medicine, and now is the time to figure out how best to incorporate genetic information into e-health records, before multiple nonstandard approaches take hold" [25]. A survey published in 2009 has identified lack of standards for data elements, terminology, structure, interoperability, and clinical decision support rules as some of the major barriers and challenges to the integration of genetic/genomic information with clinical data [9]. As information and knowledge of genetics/genomics continue to rapidly expand, providers will require point of care education and

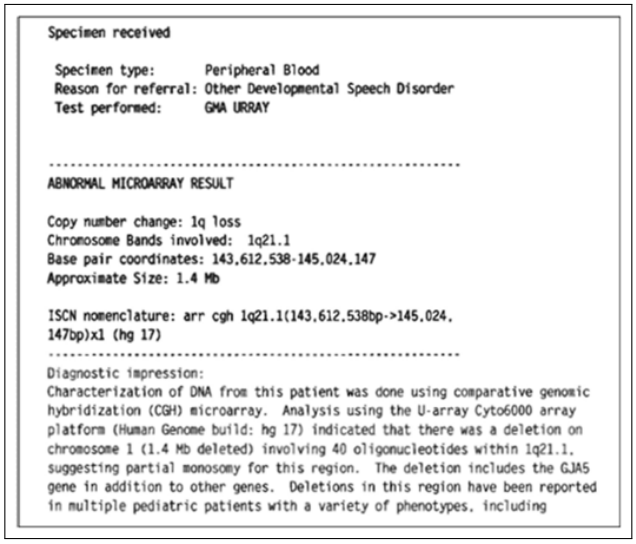
CDS system integrated into EHRs to remain current with the best practice guidelines and to take full advantage of genetic/genomic advances in medical practice. Our development effort has extended LOINC coverage for genetic sequencing test results to cytogenetics. The information models we created enable the transmission of structured constitutional cytogenetic test results electronically from the testing facilities to the ordering institution, for incorporation into the EHRs. Such integration could minimize the opportunity for misinterpretation of the results. And this can be done with existing HL7 messages and infrastructure.

```
OBR|1||PO-1001^ARUP|0040201^Genomic Microarray, U-Array Chip^99ARU-
ORDER-TEST-ID||20100702000000|20100702100909||||||201070201410
||12345^Dr.Jones|||||20080703000000|||F|||||^Other developmental speech||||||||||||||
62389-2^Chromosome analysis master panel^LN|
SPM|1|||^Peripheral blood||||||||||20100702100909
OBR|2||PO-1001-1^ARUP|62377-7^Chromosome analysis arr copy number
change panel^LN||20100702000000|20100702100909|||||201070201410|
|12345^Dr.Jones|||||201070201410|||F|||PO-1001^ARUP
OBX|1|CWE|62374-4^Human reference sequence NCBI build
id^LN||LA_X5^NCBI35^LN|||||F|201070201410|||||||||ARUP Laboratories
OBX|2|CWE|62375-1^Arr platform^LN||^U-Array
Cyto6000|||||F|201070201410|||||||||ARUP Laboratories
(... more OBXs could be placed here to represent other information in the arr
panel...)
OBR|3||PO-1001-2^ARUP|62386-8^Chromosome analysis summary
panel^LN||20100702000000|20100702100909|||||201070201410||12345^Dr.Jones|||||
201070201410|||F|||PO-1001^ARUP
OBX|1|CWE|62357-9^^Chromosome analysis result overall interpretation^LN
||LA12748-2^Abnormal^LN|||||F|201070201410|||||||||ARUP Laboratories
OBX|2|CWE|62356-1^Chromosome analysis result in ISCN expression^LN||arr
cgh 1q21.1(143,612,538bp->145,024,147bp)x1^^2.16.840.1.113883.6.299^^^^2005|
|||||F|201070201410 |||||||||ARUP Laboratories
OBX|3|CWE|48002-0^Genomic source class^LN||LA6683-2^Germline^LN|||||
F|201070201410|||||||||ARUP Laboratories
OBR|4||PO-1001-3^ARUP|62377-7^Chromosome copy number change
panel^LN||20100702000000|20100702100909|||||201070201410||12345^Dr.Jones|
|||||201070201410|||F|||PO-1001-2^ARUP
OBX|1|CWE|62378-5^Chromosome analysis copy number change type^LN||
LA14034-5^Deletion^LN|||||F|201070201410|||||||||ARUP Laboratories
(... more OBXs could be placed here to represent other information in the copy number
change panel...)
```

Figure 7: Sample HL7 version 2 message for chromosome analysis arr copy number change test result.

The standardization of genomic data representation is a vital component of a national CDS infrastructure to enable the widespread and consistent usage of genomic data and the practice of personalized medicine [10]. The information models and the set of associated LOINC codes that we created are an essential step toward the efficient use of molecular cytogenetics data in health care, decision support and research. By integrating structured test results and coded answers into a patient's EHR, best practice guidelines can be triggered for specific syndromes. Through research that tracks patient outcomes which have been correlated with genetic test results, we will be able to learn the significance of many kinds of findings. Uniformly structured genetic test results that use standard codes will enable the development and deployment of well-structured, informed, patient-specific, and genetic test specific education materials. The proper representation of genetic results will also allow development of professional publications and other online resources that can be delivered by the EHR to clinicians within the patient care work flow through integration with the infobutton standard [21, 26]. Secondary use of the combination of genetic, genomic, and clinical data as exemplified by the eMERGE project are also made possible by such integration [27].

Easy to read (clinician friendly) reports may improve patient care [28]. With structured and coded results, the receiving systems can customize the content and format of reports according to local preferences and the needs of different target audiences. For example, information that is most important to patient care such as results, clinical relevance of the tests, and recommendations can be placed at a prominent location in the report. Some laboratory technical information that is of less interest to the clinicians, such as number of cells analyzed, may be placed at a less prominent location in the report. In our LOINC panels, we created a LOINC code "recommended action", and the LOINC answer list for this code includes three values: genetic counseling recommended, confirmatory testing recommended, additional testing recommended. This structured and coded list is not part of the reports currently reported by the laboratories; we introduced this code to the cytogenetics LOINC panels with the hope that it would help promote clinician friendly reports.



```
Specimen received

Specimen type:       Peripheral Blood
Reason for referral: Other Developmental Speech Disorder
Test performed:      GMA URRAY


------------------------------------------------------------
ABNORMAL MICROARRAY RESULT

Copy number change: 1q loss
Chromosome Bands involved:  1q21.1
Base pair coordinates: 143,612,538-145,024,147
Approximate Size: 1.4 Mb

ISCN nomenclature: arr cgh 1q21.1(143,612,538bp->145,024,
147bp)x1 (hg 17)
------------------------------------------------------------
Diagnostic impression:
Characterization of DNA from this patient was done using comparative genomic
hybridization (CGH) microarray.  Analysis using the U-array Cyto6000 array
platform (Human Genome build: hg 17) indicated that there was a deletion on
chromosome 1 (1.4 Mb deleted) involving 40 oligonucleotides within 1q21.1,
suggesting partial monosomy for this region.  The deletion includes the GJA5
gene in addition to other genes.  Deletions in this region have been reported
in multiple pediatric patients with a variety of phenotypes, including
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Figure 8: Partial sample report of chromosome analysis arr copy number change.

6.1 Challenges in Naming Genetics Test Orderable

Test order names are a special problem in genetics testing in general and molecular cytogenetics in particular because different laboratories use different naming styles and different names for the same meaning. For example, they variously use the syndrome name of interest, the test methods, the target specimen, and/or the targeted genome in their names. This situation creates a problem for ordering clinicians because the actual testing varies from laboratory to laboratory and within a single laboratory over time. NCBI is working to develop a database that intends to capture the fine details of genetic test procedures by laboratory to ameliorate this problem. We do not propose a set of standard names for genetic tests or-

ders in this proposal; rather, we propose a way to convey all of the relevant information about the test that was done and its results within the test report.

The severity of the problem with test order names varies with the method type. The test order names for a conventional banding technique are relatively consistent across laboratories. For example, conventional karyotyping order names are usually based on specimen type, e.g., blood or amniotic fluid. Order names for FISH tests vary the most. Some laboratories ask the ordering providers to first choose Chromosome Analysis FISH-Metaphase test on the test requisition form, and then provide a separate menu for choosing syndromes and or probes of interest (e.g., Williams syndrome, Cri-du-chat syndrome), but do not ask the user to identify the particular genomic sequences of interest. Other laboratories use the syndrome name, the method, and the genetic variation of interest, to name their tests (e.g., "Williams syndrome, 7q11.23 deletion, FISH" and "Cri-du-chat syndrome, 5p15.2 deletion, FISH" are shown as two different test names) [29]. The first approach, which names a test by independently combining the important semantic parts at the time of test order, could be described as a post-coordinated approach, and the second strategy of combining the various parts into a single test name prior to ordering could be described as a pre-coordinated approach. For the reporting of FISH test results, we chose the post-coordinated approach, because it is simple and flexible and requires the fewest number of codes to express the essential nature of the test. A zero-to-many FISH Probe Panel reports all the FISH probes used in a FISH test.

Because arr testing targets the entire genome, the naming of arr test orders is less complicated than for FISH testing, and typically needs only the type of specimen precoordinated with the arr platform (usually commercially purchased). The arr platforms do vary considerably by laboratory so our proposed reporting specification requires both the commercially obtained microarray platform and its version number to be recorded.

One of the efforts of International Standard Cytogenomic Array Consortium (ISCA) is to develop recommendations for standards for the design, resolution and content of the cytogenomic arrays, and the design is intended to be platform and vendor neutral [30]. And while the three laboratories we worked with happened to use the same arr platform, they have named their arr tests differently, e.g., "Genomic Microarray, U-Array Chip", "Chromosomal Microarray, EmArray 60 K", and "Array Comparative Genomic Hybridization (aCGH), Whole Genome, Constitutional" [31, 32, 33]. Without communication with the cytogenetics laboratories, clinicians and patients will not be able to determine whether these tests produce comparable results based on the test names alone. We created a platform and vendor neutral LOINC code to represent the arr test, chromosome analysis microarray copy number change panel, and allow for the differences in platforms to be described within the result message.

We encourage laboratories to employ the panel names we have proposed for organizing reports as order names where they apply, but they can also continue to use their local order names which will be included in OBR-4, Universal Service Identifier, for linking the report to the originating order, but continuing effort in the cytogenetics industry to standardize cytogenomic array design and their naming will be critical in improving interoperability in ordering.

6.2 Limitations

Our analysis of cytogenetic test names and results was not exhaustive. We requested sample reports and imports from additional cytogenetics laboratories, and received them from ARUP Laboratories, Emory Cytogenetics Laboratory, and Mayo Clinic Cytogenetics Laboratory. These are large and representative cytogenetics laboratories, which are active members of ISCA. We believe the information models and LOINC codes that we developed based on the sample result reports from these three laboratories are applicable to cytogenetic result reports from all other cytogenetic laboratories; evaluations including more institutions will be needed to substantiate this assertion.

7 Conclusions

We have described how the LOINC codes for representing cytogenetics result reports were developed. The sample result reports can be dissected based on the LOINC panel structures, and can then be transmitted through HL7 v2.x messages in a coded and structured way using these LOINC codes.

The proposed LOINC codes met our objective and will allow the use of well established health informatics standards to exchange coded and structured cytogenetic test results between testing laboratories and ordering institutions. Use of standard structures and terminologies for cytogenetic results is critical for effective communication between testing laboratories and clinicians. This minimizes misinterpretation, leads to consistency, and provides the EHR systems flexibility in customizing report formats to present more clinician-friendly reports.

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