INTEGRATING CONSTITUTIONAL CYTOGENETIC TEST RESULT REPORTS INTO ELECTRONIC HEALTH RECORDS

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Genetic testing is becoming increasingly important to medical practice since the completion of the Human Genome project. To realize the full promise of personalized medicine, we need to first integrate genetic and genomic information into Electronic Health Records (EHRs) as coded and structured data using standards. However, EHRs are not ready for genomic medicine; lack of standardized information models and terminologies for genetic and genomic data representation is recognized as one of the major barriers.

In this study, we have focused on constitutional cytogenetic tests. We first evaluated the Logical Observation Identifiers Names and Codes (LOINC), the de facto vocabulary standard for representing laboratory test names and results, and identified that a gap exists in LOINC to support the integration of cytogenetic test results into EHRs. We analyzed sample clinical reports from several large cytogenetics laboratories, and developed LOINC panels and codes for representing constitutional cytogenetic test findings through the LOINC panel approach. The LOINC committee approved the cytogenetic LOINC panels and officially released them as part of the LOINC database in December 2010. We then followed the well vetted standard development process of Health Level Seven (HL7), developed and balloted a HL7 version 2 implementation guide that details how these LOINC panels are coupled with the messaging standard to transfer cytogenetic test

results over the wire. We also described the advantages of coupling the LOINC panel content to HL7 version 2 messages, and why we think this approach could be a practical and efficient way for implementers to develop interfaces that utilize standard information models bound to standard terminologies.

We have filled the gap that there were no standard information models and no standard terminologies for representing constitutional cytogenetic test results, and have developed the foundation to allow incremental enhancement in the future.

To my family Leif, Liberty, and Justice, to my parents, and to the memory of my beloved grandma, Xiuyun Wang.

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CHAPTER 1

INTRODUCTION

Statement of the Problem

The successful completion of the Human Genome Project in April 2003 marked the beginning of the "genome era." One of the great impacts that genomics has on improved patient care is its applications to diagnostics. The number of disease tests has increased from 110 to over 2,400 in the past 20 years or so; about 2,200 of them are for clinical use [1]. Tests that were uncommon a short while ago are now routinely performed at genetic testing labs all over the United States. Patients are being exposed to greater amounts of genetic information routinely. For example, newborn screening is being expanded to test for over 30 diseases depending on the state [2]. The global molecular diagnostics market was worth $6.5 billion in 2005; it will expand to $35 billion by 2015 [3]. Genetic/genomic data are becoming increasingly important for clinical decision making. Translating the knowledge from genetic/genomic discoveries into practical clinical applications is critical for realizing the potential of personalized health care and improving the health of the nation.

With genetic testing as a part of mainstream medicine, not only will clinical professionals be expected to become more genetically literate, but also the clinical information systems will be expected to manage the genetic testing results and to support the

exchange of genetic and genomic information. Currently, genetic test results exist as narrative reports; they are not integrated with the Electronic Health Records (EHRs) in most institutions. It is well recognized within the genetic testing field that standards are lacking in many aspects of the process of ordering, results reporting, and interpretation of genetic tests [4]. The format of genetic test requisitions and result reports varies from laboratory to laboratory; test results lack clarity about the clinical significance of the findings and are not clinician friendly. All of these pose huge communication issues among professionals in both laboratory and clinical settings, and could potentially lead to substandard quality control, misdiagnoses, poor healthcare decision-making or counseling and therefore a less desirable patient outcome.

Most traditional clinical information systems are not designed with incorporating genetic and genomic information in mind. Lack of standards for data elements, terminology, structure, interoperability, and clinical decision support rules is one of the major barriers and challenges to the integration of genetic/genomic information with clinical data [5].

Objectives

Standard terminologies alone are not sufficient to unambiguously exchange data between heterogeneous systems, to share decision support logic, or to support the secondary use of clinical data. Information models, which provide semantic structure of the data representation and specify how vocabulary should be bound to each slot of the semantic structure, are crucial for achieving interoperability. Information models that are tightly coupled with standard terminologies put discrete data elements into meaningful

context, which can then be shared consistently across systems and institutions. Together, standardized terminologies and information models are one of the fundamental building blocks for realizing semantic interoperability.

This study has two specific aims as outlined below:

Aim 1: Develop information models to represent the semantics of constitutional cytogenetic test results, and use the models to guide the creation of LOINC codes to represent the test results. This aim is not to try to develop a list of standard terminologies and information models that are comprehensive, but rather to focus on developing terminologies and information models that are flexible and sustainable.

Aim 2: Develop a standard implementation guide for messaging cytogenetic test results, which uses the information models and the LOINC codes as the interoperability building blocks, and follows the well vetted standard development process of Health Level Seven (HL7). The implementation guide specifies how cytogenetic test results should be transmitted over the wire. It not only fits the rapid changing and evolving nature of the field of genetic testing but also is able to take advantage of the existing EHR infrastructure that could lead to rapid adoption and implementation in the United States.

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CHAPTER 2

BACKGROUND

Cytogenetic Tests

Genetic tests are greatly impacted by the exponential growth of genetic research discoveries and technological innovations. According to GeneTests, a genetic test is defined as the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect a heritable disorder. This can be accomplished by directly examining the DNA and RNA that make up a gene (direct testing), looking at markers co-inherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing) [1]. It is also important to note that genetic tests are increasingly being applied to acquired somatic changes to cells, particularly in cancer, so the definition limiting testing to heritable disorders is increasingly obsolete. This has been reflected in the definition adopted by the Genetic Testing Registry (GTR) [2]. The National Institutes of Health (NIH) established the GTR to serve as the single public resource to provide detailed information about the 1600+ genetic tests for patients and consumers; NIH made the registry available to the public in early 2012. GTR defines a genetic test as the analysis of DNA, RNA, chromosomes, proteins, or metabolites to detect genotypes, mutations, chromosomal changes, or levels of gene expression in a human sample [2]. Because of the broad scope and fast

evolving nature of genetic testing, it is impractical to tackle standard information models and terminologies for all genetic tests at once. This dissertation research focuses on cytogenetic testing—one domain within the field of genetic testing. However, the goal is that we could easily generalize the approach we have used to develop the information models and standard terminologies for cytogenetic test results and apply that approach to other genetic testing domains.

Cytogenetic tests evaluate whole chromosomes in 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 [3]. The emerging field of cytogenomics includes conventional cytogenetics, which uses chromosomal banding techniques, 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 [4]. Cytogenomic microarray circumvents a limitation of FISH as it does not require foreknowledge of the chromosomal loci being evaluated [5].

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 [5]. Conventional and molecular cytogenetics technologies are often used to complement each other or used together in this evolving practice.

Cytogenetic Test Result Reporting

Test names vary significantly between different genetic laboratories and this lack of consistency can be confusing. Individuals unfamiliar with a specific cytogenetic test name may need to inquire directly with laboratory personnel. Standardizing the cytogenetic test names and representing them using universal identifiers would save unnecessary work, improve efficiency of communication, enhance data interoperability, prevent possible ordering mistakes, and ultimately improve patient care.

Unlike other laboratory reports, the majority of genetic tests including cytogenetic tests are now reported as a narrative report. These narrative reports are sent through HL7 version 2 (V2) messages and are stored as narrative text in EHRs. Genetic test results are integrated with other clinical data for full clinical assessment. The current narrative format traps the information in the language of the report, which makes it difficult to find a specific detail without reading through the report and difficult to enable computerized decision support. These narrative reports vary from laboratory to laboratory, which sometimes results in incomplete communication between testing laboratories and clinicians, which could result in compromised patient care and increased costs.

The format of cytogenetic test result reports has been more standardized among different cytogenetics labs in comparison with formats of result reports used by other types of genetic tests. This is mainly because cytogenetics labs have been using the International System for Human Cytogenetic Nomenclature (ISCN) as the gold standard of describing chromosome aberrations for almost 40 years. ISCN is critical in reporting cytogenetic test results; it was created by the International Standing Committee on Human Cytogenetic Nomenclature to represent the outcome of cytogenetic tests [6]. 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 [7,8].

ISCN provides a list of symbols and abbreviated terms in conjunction with a set of rules, such as *p* for short arm of the chromosome, *q* for long arm of the chromosome, *cen* for centromere, *del* for deletion, *ish* for in situ hybridization, and plus sign (+) for gain, etc. A cytogenetics test result defined in the ISCN notation provides precise, unambiguous descriptions of the cytogenetic findings. Example ISCN expressions are: "46,XX", which indicates a normal female; "47,XY,+21", which indicates a male with trisomy 21 (an extra copy of chromosome 21, commonly known as Down syndrome). 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 [6].

The International Standing Committee on Human Cytogenetic Nomenclature has traditionally updated ISCN every 10 years. However, as the field of cytogenetics continues to include several molecular-based technologies, the latest revision of ISCN was published in 2009—four years after the previous version—to provide more up to date and accurate descriptions of the new technologies, e.g., a new chapter was added with nomenclature examples describing copy number detection due to rapid advancement in microarray technology [9].

LOINC

Consolidated Health Informatics (CHI) initiative adopted Logical Observation Identifiers Names and Codes (LOINC) system as the standard vocabulary for observation identifiers for use in electronic exchange of laboratory test results in 2004 [10]. HL7 V2 is considered to be the most widely implemented standard for healthcare information in the world. LOINC was initially designed to provide universal identifiers for observations sent in HL7 messages. Specifically, LOINC provides a code system for the observation identifier field (OBX-3) of the HL7 observation reporting message. Other fields in the HL7 messages provide additional semantic structures that are needed to reflect a model of laboratory testing orders and results observations. However, LOINC is now being used in other messaging standards, such as Digital Imaging and Communication in Medicine (DICOM) ultrasound messages and Clinical Data Interchange Standards Consortium (CDISC) pharmaceutical industry messages [11].

The Regenstrief Institute is responsible for the development and maintenance of the LOINC database as well as the Regenstrief LOINC Mapping Assistant (RELMA) tool. RELMA is a program that provides LOINC users with functionalities such as browsing, searching, and mapping. Both LOINC and RELMA are freely available to the public [12]. A new LOINC web search tool is now also available for users to search LOINC codes online [13]. Since the Regenstrief Institute first released the LOINC codes to the internet in 1996, LOINC content has continued to grow and LOINC has become the most widely adopted standard for laboratory test result names in the United States and internationally. The latest LOINC database version 2.38, which was released in Decem-

ber 2011, contains 68,350 terms. LOINC has been translated into several languages, and there are LOINC users in at least 145 countries.

Each LOINC term consists of a six-part structure: component (analyte), kind of property, time aspect (timing), system (sample), type of scale, and type of method. Examples of component (analyte) include potassium and hemoglobin. Kind of Property contains information about what kind of property was measured about the component, such as a mass concentration. Timing describes whether the measurement is an observation at a moment of time, or an observation integrated over an extended duration of time, such as 24-hour urine. The type of sample is urine, blood, and skin, etc. The type of scale specifies whether the measurement is quantitative, ordinal, nominal, or narrative. Method describes the process used to produce the result or other observation, and is optional in the six-part structure. Each LOINC part can be made of subparts. A fully specified LOINC name uses a colon character, ":", to connect its six parts and a carat, "^", to connect the subparts, for example, ABO group:Type:Pt:Bld^donor:Nom (ABO group in blood from donor). For convenience, a LOINC term may also have a unique short name in addition to its fully specified long name.

LOINC panels are used to represent collections that have enumerated discrete contents by creating LOINC panel terms that are linked to an enumerated set of child elements. The child elements are LOINC terms or panel terms themselves, the latter allows representation of a fully nested hierarchical structure. A LOINC panel child element has an attribute of cardinality, which specifies the allowable number of repetitions for an item.

LOINC answer lists are used to define allowable answers to a LOINC term. Answer lists could be an enumerated list of answers that reside internally in LOINC with an Object Identifier (OID) assigned to identify the entire answer list and a unique identifier assigned for each answer option. Answer lists could also be pointing to an external answer list uniquely identified by an OID and code system.

Health Level Seven

HL7 is one of several American National Standards Institute (ANSI) accredited Standards Development Organizations (SDO) operating in the healthcare arena. HL7 focuses on the data exchange requirements of the entire health care organization. It provides standards for interoperability that improve care delivery, optimize workflow, reduce ambiguity, and enhance knowledge transfer among healthcare providers, government agencies, the vendor community, fellow SDOs, and patients [14].

An HL7 message is a hierarchical structure associated with a trigger event. A trigger event is an event in the real world of health care that creates the need for data to flow among systems, such as registering a patient. An HL7 message is a collection of segments; it includes the rules of repetition and inclusion for those segments. Examples of segments include Message Header (MSH), Patient Identification (PID), Observation/Result (OBX), and Observation Request (OBR). An HL7 segment is a group of fields each of which conforms to a particular data type. Fields can consist of components according to their data type definitions, and components may consist of subcomponents to represent complex structure. HL7 V2 messages use delimiters such as “|”, “^”, and “&” to separate fields, components, and subcomponents respectively. A carriage return, “<cr”>, is used to terminate a segment record. HL7 data type definitions are critical to

constructing HL7 V2 messages properly and to understanding and parsing the data contents of an HL7 field.

HL7 V2 was designed using an 80/20 approach to solve clinical interfacing problems in a flexible manner [15]. This practical solution led to the widespread acceptance of the standard, but also has led to its own challenges. The lack of precision (vagueness and flexibility allowed in the standard) is among some of the main challenges or weaknesses of the current HL7 V2 standards. Even though HL7 messages for order entry and results reporting were not designed with supporting genetic tests in mind, because of the flexibility allowed in HL7 V2 standards, we know we will be able to use HL7 V2 to transmit genetic test results reporting messages with customization. However, to allow all implementers, including vendors, laboratories, and healthcare facilities, to define interfaces for genetic test result reporting consistently, we need a mechanism to unambiguously represent the semantic relationships of observations contained in a clinical report and to couple it with the structure of HL7 V2 messages.

HL7 implementation guides are balloted through HL7; they are implementation oriented and provide more detailed instructions for a specific use case. 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 [16]. This guideline was sponsored by the Clinical Genomics Work Group. The genetic variation model contains a set of four nested LOINC panels. Genetic Analysis Master Panel is the parent panel, which has exactly one Genetic Analysis Summary Panel and zero-to-one Genetic Analysis Discrete Result Panels. The Genetic Analysis Discrete Result Panel has zero-to-many DNA

Analysis Discrete Sequence Variation Panels. Intermountain Healthcare and Partners Healthcare Center for Personalized Genetic Medicine have developed a pilot implementation of the guideline. The two organizations 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 [17]. However, this implementation guide covers only genetic test results for the identification of DNA sequence variations contained within a gene; it does not support the reporting of cytogenetic test results.

HL7 has started the development of version 3 (V3) standards in the late 1990s to address problems inherent in V2 standards. HL7 V3 messages are derived from the underlying HL7 Reference Information Model (RIM); this model based standard provides consistency across the entire standard, which is lacking in HL7 V2. HL7 V3 also has fewer message options, which is more rigorous than V2. However, HL7 V3 messages have not been widely adopted within the U.S. as a means to exchange clinical data. As of today, HL7 V3 has mainly been adopted by regions or environments where V2 was rarely or never used. In the U.S., because HL7 V2 has been so heavily implemented and supported by almost all EHR systems, it will not fade away any time soon. HL7 V2 and V3 will likely coexist, especially where clinical documents are used, e.g., an HL7 V3 Clinical Document Architecture (CDA) document could be sent in an HL7 V2 message. HL7 V3 CDA, a document markup standard that specifies the structure and semantics of clinical documents for the purpose of exchange, has gained wide acceptance worldwide, and within U.S. as well, largely driven by recent government legislation that specifies Meaningful Use [18]. However, CDA was designed specifically for clinical documents; HL7

V2 and LOINC are the most widely implemented standards for laboratory orders and result reporting.

Clinical Decision Support

Clinical decision support (CDS) systems have shown great promise for reducing medical errors and improving patient care. The Institute of Medicine identified computerized clinical decision support as one of eight core functionalities that a successful EHR should incorporate to promote greater safety, quality, and efficiency in health care [19]. When effectively used, CDS can significantly improve clinical practice as shown in over 90% of randomized controlled trials [20]. CDS is one of the core rationales for why the healthcare industry is now driving toward widespread use of EHRs.

CDS provides clinicians, staff, patients, or other individuals, with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and healthcare. Knowledge-based CDS systems typically contain three parts: the knowledge base, the inference engine, and a mechanism to communicate with the user [22]. Computer alerts at the time of order entry in a computerized provider order entry system, such as dose range checking for medications, drug-drug interactions, and drug-allergy checking, can help catch a critical source of human error [23,24]. CDS could potentially guide physicians toward ordering the most appropriate and cost effective tests at the point of ordering. Randomized trials have shown that computerized reminders and prompts increase the use of preventive care in both the outpatient and inpatient setting [25]. CDS also yields increased adherence to guideline-based care [26].

As personalized medicine enters the healthcare delivery system, there will be increased use of molecular tests and greater reliance on healthcare information systems for

decision support. Enhancing the use of CDS tools will provide just-in-time education and support the optimal use of genetics and genomics in health care, which will help to overcome the shortage of healthcare professionals and public health providers trained in genetics [27]. For example, tools like "infobuttons" could be implemented to establish links between coded problems in the problem list and relevant on-line genetic resources [28]. CDS can also trigger execution of a best practice guideline for a particular syndrome, such as the guidelines for children with Down syndrome [29].

The combination of genetic/genomic information and EHRs provide a potentially rich data source for discovering correlations between diseases and for genome-wide association analysis. In addition to secondary use of EHR data for clinical research, the same approach can now be used to guide real-time clinical decisions, when existing literature is insufficient to guide the clinical care of a patient [30].

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CHAPTER 3

CYTOGENETICS LOINC CODES EVALUATION

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Abstract

Genetic testing is becoming increasingly important to medical practice. Integrating genetics and genomics data into electronic medical records is crucial in translating genetic discoveries into improved patient care. Information technology, especially Clinical Decision Support Systems, holds great potential to help clinical professionals take full advantage of genomics advances in their daily medical practice. However, issues relating to standard terminology and information models for exchanging genetic testing results remain relatively unexplored. This study evaluates whether the current LOINC standard is adequate to represent constitutional cytogenetic test result reports using sample result reports from ARUP Laboratories. The results demonstrate that current standard terminology is insufficient to support the needs of coding cytogenetic test results. The terminology infrastructure must be developed before clinical information systems will be able to handle the high volumes of genetic data expected in the near future.

Introduction

The successful completion of the Human Genome Project on April 14, 2003, marked the beginning of the "genome era," and subsequent gene discoveries are leading to major advances in both diagnosis and treatment. The number of clinically available genetic tests is rapidly growing. When GeneTests, supported by the National Institutes of Health, started tracking laboratories providing genetic tests in 1993, there were 110 disease tests available. Today there are about 1700 disease tests available [1]. Genetics is becoming increasingly important to health care providers and genetic testing is being integrated into medical practice in many areas of medicine. Even though genomic advances promise to improve patient care, the explosion of information and knowledge in the areas

of genetics, genomics, and health care can be demanding. This information and knowledge explosion, coupled with the lack of integration of genetic testing information with traditional patient data, presents great challenges if we are to take full advantage of genomic advances in medical practice.

Many physicians have reported a lack of basic knowledge and confidence about medical genetics, which limits their ability to appropriately counsel their patients and accurately interpret genetic tests [2]. Missed opportunities for health professionals to educate patients and families regarding genetics have been identified [3]. In addition to the competency of medical staff, the variation and format of test requisitions and result reports have contributed to poor communication between testing laboratories and clinicians [4]. The quality of patient care may be compromised as a consequence.

The importance of standardizing genetic test result reports is well recognized. Efforts have already begun to address this issue within the laboratory testing industry. For example, some model reports for molecular genetic testing have been developed and the College of American Pathologists (CAP) provides a checklist for result reporting [2,5]. However, little has been done to address how to use information technology to improve the use of genetic test results in medical practice. In particular, the use of standard controlled terminology and information models for exchanging and storing genetic test result reports in Electronic Medical Records (EMRs) remains relatively unexplored.

It is widely agreed that information technology, especially Clinical Decision Support Systems (CDSS), has the potential to reduce medical errors, and to improve quality, safety, and efficiency of health care. Bringing genetic tests results into the patient's EMR is one of the essential first steps in translating genetics and genomic knowledge into daily

medical practice. However, it will be very difficult to apply decision support if the genetic test results are simply transmitted and stored as narrative text or as images in the EMR. Establishing standard logical representations for genetic data using controlled terminologies and information models is a prerequisite to establishing genetic CDSS as part of an EMR system.

The Logical Observation Identifiers Names and Codes (LOINC) system was adopted by the Consolidated Health Informatics (CHI) initiative as the standard vocabulary for observation identifiers for use in electronic exchange of laboratory test results. Health Level Seven (HL7) version 2 is considered to be the most widely implemented standard for healthcare information in the world. LOINC was designed to provide universal identifiers for observations sent in messages in data exchange standards like HL7 and Digital Imaging and Communication in Medicine (DICOM). For example, LOINC provides a code system for the observation identifier field (OBX-3) of the HL7 observation reporting message. Other fields in the HL7 messages provide additional semantic structures that are needed to reflect a model of laboratory testing orders and results observations. Since the first release of LOINC over 10 years ago, LOINC content has continued to grow and LOINC has become the most widely adopted standard for laboratory test result names in the United States and internationally.

Clinical cytogenetics is the study of the genetic constitution of individuals by examining the structure and organization of chromosomes. Chromosome tests were introduced into clinical practice in the late 1950s. Constitutional cytogenetic tests can detect pre-existing numerical and structural abnormalities prenatally or after birth. Chromosomal abnormalities have been found to be the etiology for a number of multiple congenital

anomaly syndromes as well as isolated mental retardation and developmental delay. Certain chromosomal abnormalities are consistently associated with medical conditions that require screening and management for the affected patient. Given their rarity and the lack of readily available clinical information, these conditions present excellent opportunities for CDSS.

The International System for Human Cytogenetic Nomenclature (ISCN) was created by the International Standing committee on Human Cytogenetic Nomenclature to represent the outcome of cytogenetic tests. The latest version of ISCN was published in 2009. One of the aims of ISCN is to prevent confusion in reporting research cytogenetics results. ISCN is accepted as a standard within the industry. It specifies the nomenclature to describe karyotypes, chromosome abnormalities, in situ hybridization, etc. The CAP checklist for cytogenetics includes an item to assure that current ISCN is used correctly in a final report.

The goal of the current study is to formulate a model for the electronic exchange of coded cytogenetic test results and to determine how LOINC codes fit into the model, and to evaluate whether current LOINC codes are adequate to support this use case.

Materials and Methods

The latest LOINC database release Version 2.26 was selected as the basis for this evaluation. This version contains 53,344 terms. We first searched the LOINC database using RELMA (a mapping and browsing tool provided with the LOINC database) to retrieve genetic related LOINC concepts. We used the key word “MOLPATH” to select the relevant content. “MOLPATH” represents Molecular Pathology, the class under which genetic related LOINC terms are grouped. To confirm the search results, we also

searched the LOINC table directly. The LOINC table was filtered using “MOLPATH” and any of its subclasses as the filter values for the “class” column. The subclasses of MOLPATH are “MOLPATH.MUT”, “MOLPATH.DEL”, “MOLPATH.TRISOMY”, “MOLPATH.TRNLOC”, “MOLPATH.TRINUC”, “MOLPATH.REARRANGE”, “MOLPATH.GENERAL”, and “MOLPATH.MISC”. The “class” filter was also used to select three additional classes: “PANEL.MOLPATH”, “HL7.GENETICS”, and “PANEL.HL7.GENETICS”. The same number of LOINC terms was returned from the filter results as from the original RELMA query. We then manually went through each of the genetic LOINC concepts to select the ones that are specifically for cytogenetic testing.

To evaluate whether the current LOINC terminology is sufficient to represent constitutional cytogenetic test names and their results, we tried to represent a list of key data elements found in cytogenetic result reports by using the existing LOINC concepts. We obtained sample constitutional cytogenetic test result reports from the Cytogenetics Section of ARUP Laboratories. ARUP is a national clinical and anatomic pathology reference laboratory owned by the University of Utah [6]. The sample result reports were chosen so they would cover tests that were done using different cytogenetic techniques including: conventional G-banding, fluorescence in situ hybridization (FISH), and microarray based comparative genomic hybridization (array-CGH). The sample reports also represented a variety of results, including normal, abnormal, and findings of unknown clinical significance. We examined these sample result reports and extracted a list of key data elements that should be coded. We also obtained the names of constitutional cytogenetic tests offered by ARUP from its online test menu.

Results

Table 2.1 shows the list of key data elements extracted from the constitutional cytogenetic test result reports that should be coded. We did not include some standard data elements in lab result reports, such as patient date of birth, sex, the specimen type, specimen collection date, reason for referral, etc. These elements should be sent in other fields in the HL7 message, and should not be sent as test results in the observation segment using LOINC codes.

The constitutional cytogenetic tests offered by ARUP are listed in Table 2.2.

A total of 1001 genetic related LOINC terms were found in the database. Among these terms, the majorities were related to mutation analysis; only 36 terms were cytogenetic test related concepts. The first part of the LOINC name is the component or analyte measured. Table 2.3 lists the 20 distinct LOINC components from the 36 LOINC names. Some of the components were used in several LOINC names in combination with different systems, properties, scales, or methods.

We found that the current LOINC terms for cytogenetic tests are not consistent with how the ARUP cytogenetic tests are named or with how the results are represented in actual reports. The existing LOINC terms are not consistent with the vocabulary needed to represent ARUP cytogenetic test names and results.

To report a chromosome analysis result for a male with Trisomy 21 (Down syndrome), the ARUP result report includes “Chromosome Analysis, Peripheral Blood” as the test name. This test name could be mapped to the LOINC code “Karyotype:Prid:Pt:Bld/Tiss:Nar”. For the test result, ARUP reports it as “47,XY,+21”, which is the ISCN representation for male, Trisomy 21. The existing LOINC codes do not support

this reporting style. Instead, they attempted to pre-coordinate the findings into the result names, e.g. *Chromosome 21 trisomy:Arb:Pt:Bld/Tiss:Ord:Cytogenetics*. This style of pre-coordination implies that the value of the result for this test as named by LOINC would be "Present" or "Absent."

For FISH studies, LOINC codes exist for Chromosome analysis, FISH-Interphase, but no codes exist for Chromosome Analysis, FISH-Metaphase. No codes are currently available to properly represent the results for any of the common microdeletion syndromes using either the LOINC variable approach or the panel approach. For example, consider DiGeorge/Velco-Cardio-Facial syndrome with the ISCN representation "ish del(22)(q11.2q11.22)(HIRA-)". To represent this finding using a panel approach, we would need a LOINC code that pre-coordinates the 22q11.2 deletion into the LOINC name. To represent it using the variable approach, a LOINC term like "chromosome analysis FISH result" would need to be created.

No LOINC codes currently exist to represent the array-CGH tests and their results.

Discussion

The number of terms in the latest LOINC release for genetic test observations, especially cytogenetic tests, is minimal. We suspect that the existing LOINC terms are not being used in production systems because the existing LOINC terms and what is being reported from ARUP imply very different models of representation. These terms do not match well with how the tests are named and how the test results are reported.

Recognizing the importance of genetic test result reporting, the LOINC committee recently began developing terms for representing genetic variations. However, there

is no specific section in the LOINC Reference Manual that discusses names and codes for cytogenetic tests. We plan to propose developing the needed cytogenetic codes in partnership with the LOINC committee.

Pre-coordination vs. Post-coordination

The majority of existing LOINC terms for cytogenetic tests are taking the pre-coordination approach. The current style of LOINC terms seems to have been created to ask questions like whether a given abnormality is found, e.g. 18q chromosome deletion:Prid:Pt:Bld/Tiss:Nom:Molgen, with the expected answers being "Present" or "Absent". Continuing this style of LOINC name creation will be problematic, not only for the representation of cytogenetic test results but also for the representation of genetic test results in general. Due to the ever growing and changing nature of this field, this pre-coordinated style of name creation will likely lead to a large number (and potentially limitless) of test names being created. For example, the U-Array Chip that ARUP currently uses for its array-CGH test contains close to 150 targeted regions and this number will continue to grow as higher density chips come into practice. In order to avoid combinatorial explosion, a post-coordinated style would be more appropriate for creating LOINC concepts for genetic testing as it will be more sustainable and flexible.

ISCN and Coded Expression Data Type

Compared to molecular genetic tests results, the advantage that cytogenetic test result reporting has is that ISCN has been the gold standard for describing chromosome aberrations for almost 40 years. ISCN provides a list of symbols and abbreviated terms in adjunction with a set of rules, which can be used in the description of chromosomes

and chromosome abnormalities, such as *p* for short arm of chromosome, *q* for long arm of chromosome, *cen* for centromere, *del* for deletion, *ish* for in situ hybridization, and plus sign (+) for gain, etc.

Data that are expressed in ISCN nomenclature need to be distinguished from either string values or concepts from a code system. Typical behaviors that are expected for coded concepts do not apply to ISCN expressions. This situation is the use case that would justify a new "coded expression" data type for use in HL7 messages. It might also suggest the need for a new type of scale in the LOINC terminology. When receiving systems encounter coded expressions, tools will need to parse the data rather than to do terminology look ups. This would also imply the need for a new query engine that could query against the ISCN expressions. For example, as new knowledge becomes available it would be desirable to run a query to identify all patients who have chromosome abnormalities that were believed to be clinically insignificant or that have unknown clinical significance at the time of testing where a revised report should be issued. The results review applications will also need to be able to present this new type of data rather than treating them the same as simple name-value pairs.

Array-CGH

Array-CGH merges molecular diagnostics with traditional chromosome analysis and is transforming the field of cytogenetics. Array-CGH holds the promise of being the initial diagnostic tool in the identification of visible and submicroscopic chromosome abnormalities in mental retardation and other developmental disabilities [7–9]. Therefore, clinical information systems should anticipate receiving more array-CGH results in the

very near future. The LOINC standard should examine this rapidly growing area and develop codes for microarray based laboratory tests.

Terminology and Information Models

The LOINC terminology without the context of an information model is not sufficient to unambiguously exchange cytogenetic test results. The LOINC codes need to be developed in the context of an information model, which is similar to putting vocabulary terms into meaningful sentence structures. In addition to the LOINC standard, other bioinformatics standard terminologies such as ISCN are necessary to represent the detailed results of cytogenetic tests.

Limitations

Our evaluation may be limited due to the fact that there is lack of industry wide cytogenetic result report standards available. As a consequence our analysis is based on sample result reports from ARUP only. However, because ARUP result reports contain all the data elements listed on the CAP checklist (which represents the industry standard), this limitation is likely minimal.

Another limitation is that the list of key data elements that we included for analysis is not complete. We did not extract data elements from the free text sections of the report such as the “diagnostic impression” and “recommendation” sections of the reports. This means that our evaluation of current reporting limitations is likely conservative.

Conclusion and Future Work

Current LOINC terminology is insufficient to support the needs of coding cytogenetic test results. With genetic testing becoming an increasingly important part of the daily medical practice, we need to develop this essential infrastructure before clinical information systems will be able to handle high volumes of genetics data.

This study was an initial step in integrating cytogenetic test result reports into EMRs. It demonstrated that a gap exists in LOINC in supporting such integration. Work needs to be done to extend LOINC to cover cytogenetic tests and to continue to expand the codes needed for the broader field of genetic variation testing. Since it is the CHI designated standard for laboratory tests, we suggest enhancing and extending LOINC to represent cytogenetics test result reports rather than creating them in some other existing terminology.

Further analysis needs to be done to develop new LOINC codes and information models to represent the constitutional cytogenetic test result reports. The analysis needs to be expanded to include result reports from other laboratories besides ARUP. Structuring the diagnostic impression and recommendation section of the result report needs to be addressed as well. Our hope is that this will lead to consistency in reporting results, in addition to simplifying access to and understanding of interpretation of those results.

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Table 2.1. Key data element in constitutional cytogenetic test result reports

Data Element
Test Performed
Chromosome Result (expressed in ISCN)
FISH Result (expressed in ISCN)
Array-CGH Result (expressed in ISCN)
Number of cells counted
Number of colonies counted
Number of cells analyzed
Number of cells karyotyped
ISCN Band Level
Banding Method
Copy number change
Chromosome bands involved
Base pair coordinates

Table 2.2. Constitutional cytogenetic tests offered by ARUP

Test #	Test Name
0097779	Prenatal FISH (Chromosomes X, Y, 13, 18 &21)
0097615	Chromosome Analysis, FISH-Metaphase
0092615	Chromosome Analysis, FISH-Interphase
0040201	Genomic Microarray, U-Array Chip
0097640	Chromosome Analysis, Peripheral Blood
0097601	Chromosome Analysis, Amniotic Fluid
0097610	Chromosome Analysis, Chorionic Villus Sampling (CVS)
0097620	Chromosome Analysis, Fetal Blood (PUBS)
0097645	Chromosome Analysis, Products of Conception (POC)
0097655	Chromosome Analysis, Skin Biopsy
0097650	Rule Out Mosaicism

Table 2.3. Distinct LOINC components from the 38 existing cytogenetic test related concepts

Test #	Test Name
0097779	Prenatal FISH (Chromosomes X, Y, 13, 18 &21)
0097615	Chromosome Analysis, FISH-Metaphase
0092615	Chromosome Analysis, FISH-Interphase
0040201	Genomic Microarray, U-Array Chip
0097640	Chromosome Analysis, Peripheral Blood
0097601	Chromosome Analysis, Amniotic Fluid
0097610	Chromosome Analysis, Chorionic Villus Sampling (CVS)
0097620	Chromosome Analysis, Fetal Blood (PUBS)
0097645	Chromosome Analysis, Products of Conception (POC)
0097655	Chromosome Analysis, Skin Biopsy
0097650	Rule Out Mosaicism

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CHAPTER 4

CYTOGENETICS LOINC CODES DEVELOPMENT

Abstract

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.

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.

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.

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.

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 [3–5].

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 cy-

togenetic 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.

Background

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 microsco-

py.[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].

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.

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 re-

sult 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.

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.

Model Description

We created three information models based on the sample clinical reports from ARUP, Mayo, and Emory cytogenetics laboratories. Figures 3.1 to 3.3 show the infor-

mation 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.

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 3.4. Chromosome analysis master panel, 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.

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 break-point 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.

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 3.5 shows the HL7 version 2.5.1 representation of the G-banding chromosome analysis report presented in Figure 3.6. Figure 3.7 shows the HL7 v2.5.1 message for the arr report of copy number changes presented in Figure 3.8.

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* o*verall interpretation*"; the concept for "*Abnormal*" is placed in OBX-5 as the value. Figure 3.9 illustrates how the cytogenetic LOINC codes fit into the nested OBR and OBX structure in HL7 version 2 messages.

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.

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 genet-

ics/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.

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 combina-

tion 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: g*enetic 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.

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 orders 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 C*hromosome 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 pre-coordinated 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"* [29,31–32]. 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.

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.

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.

Acknowledgments

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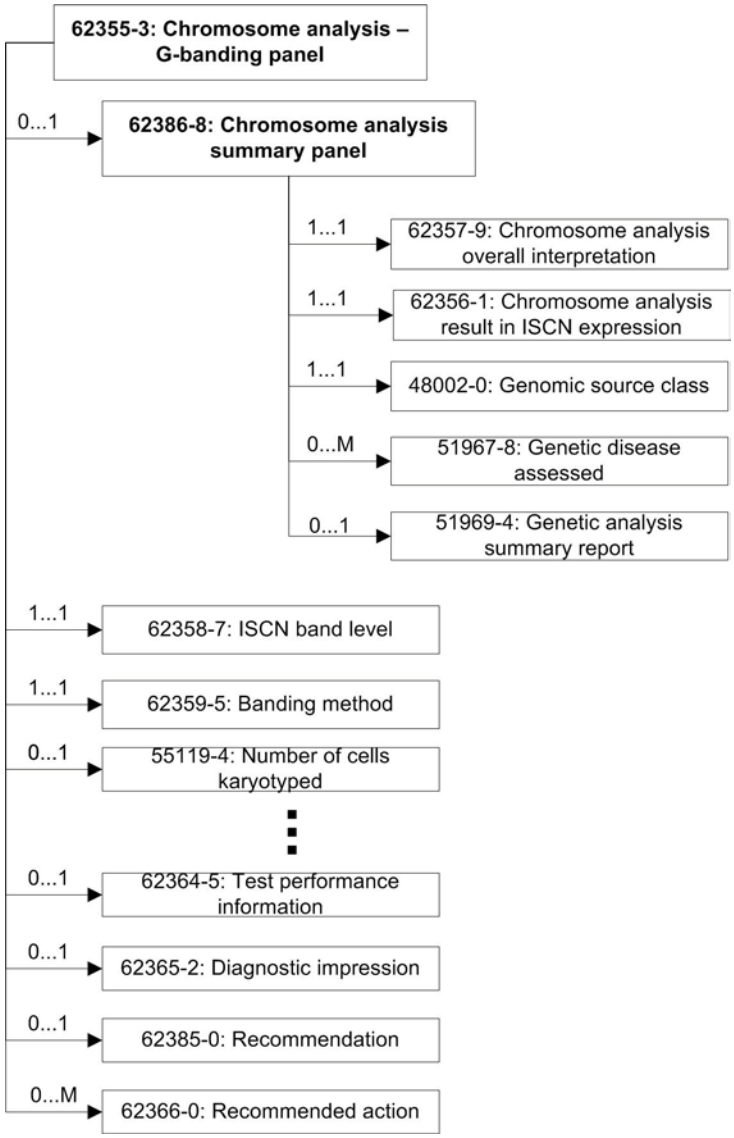


Figure 3.1. Chromosome analysis G-banding panel

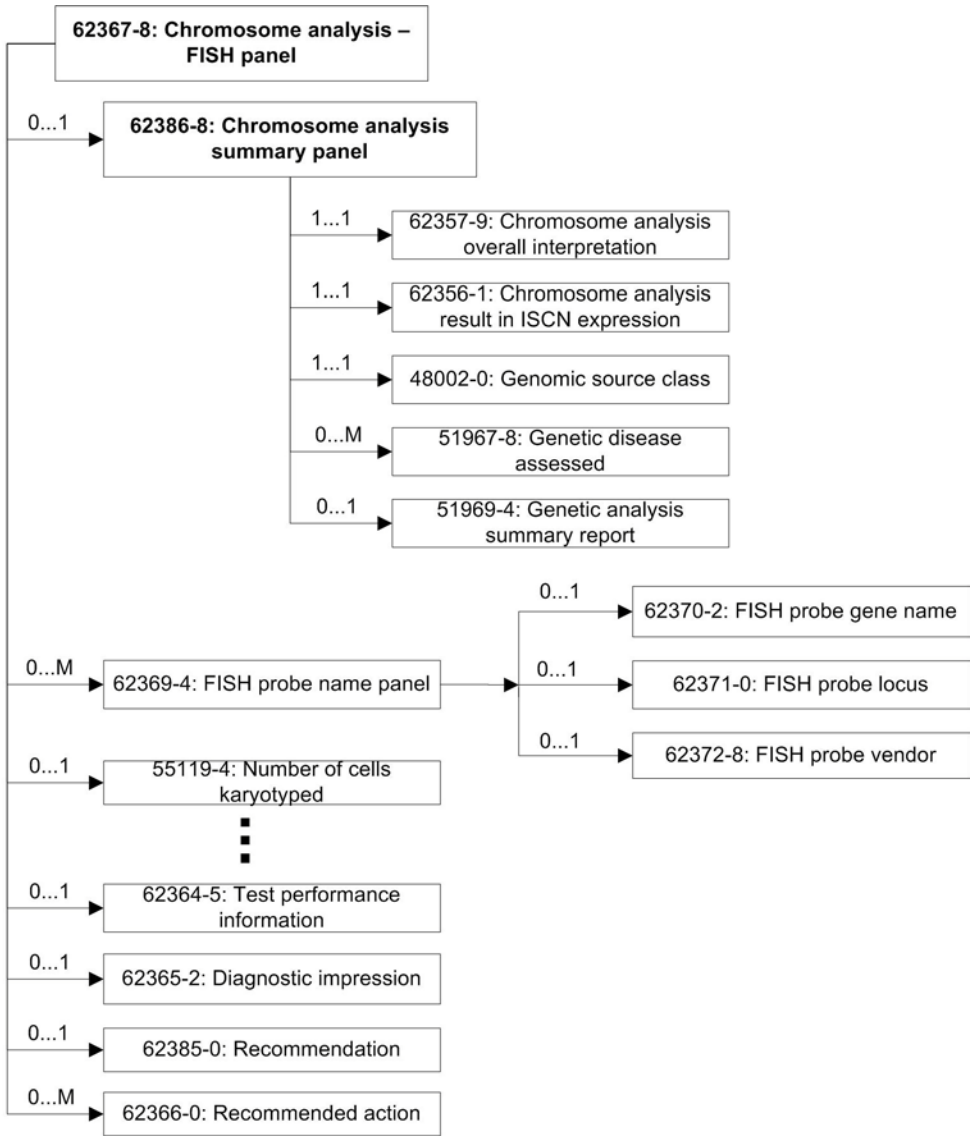


Figure 3.2. Chromosome analysis FISH panel

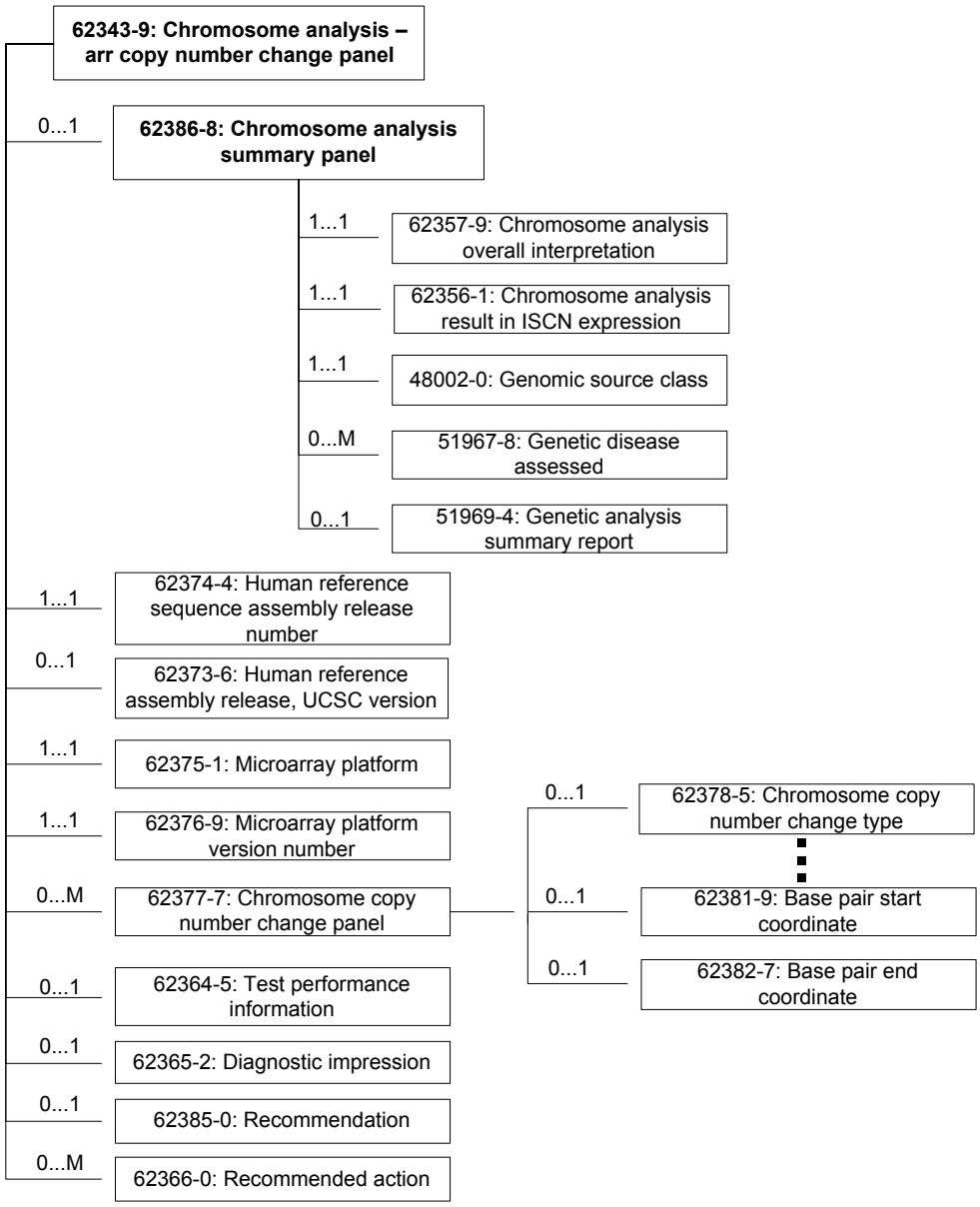


Figure 3.3. Chromosome analysis arr copy number change panel

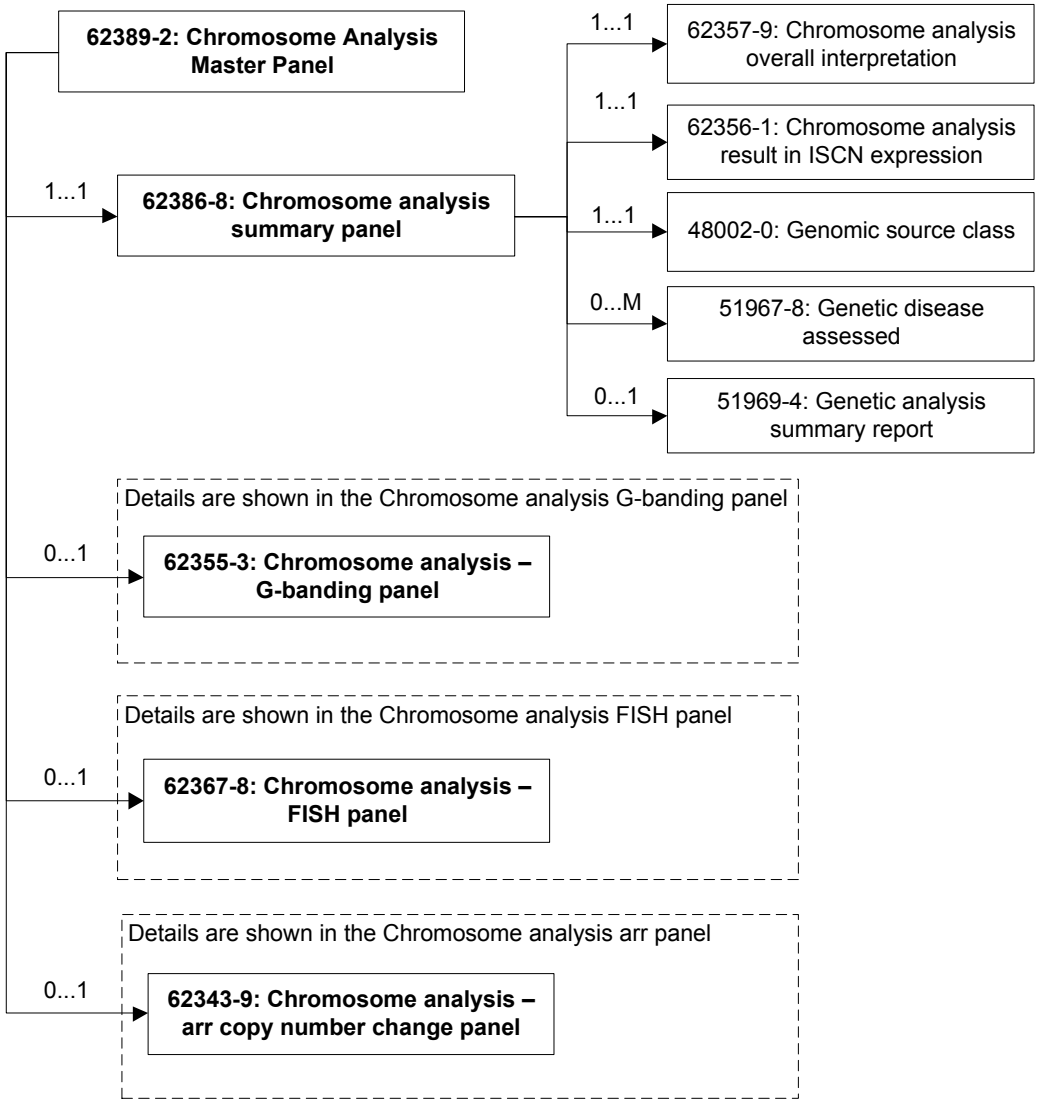


Figure 3.4. Chromosome analysis master panel

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

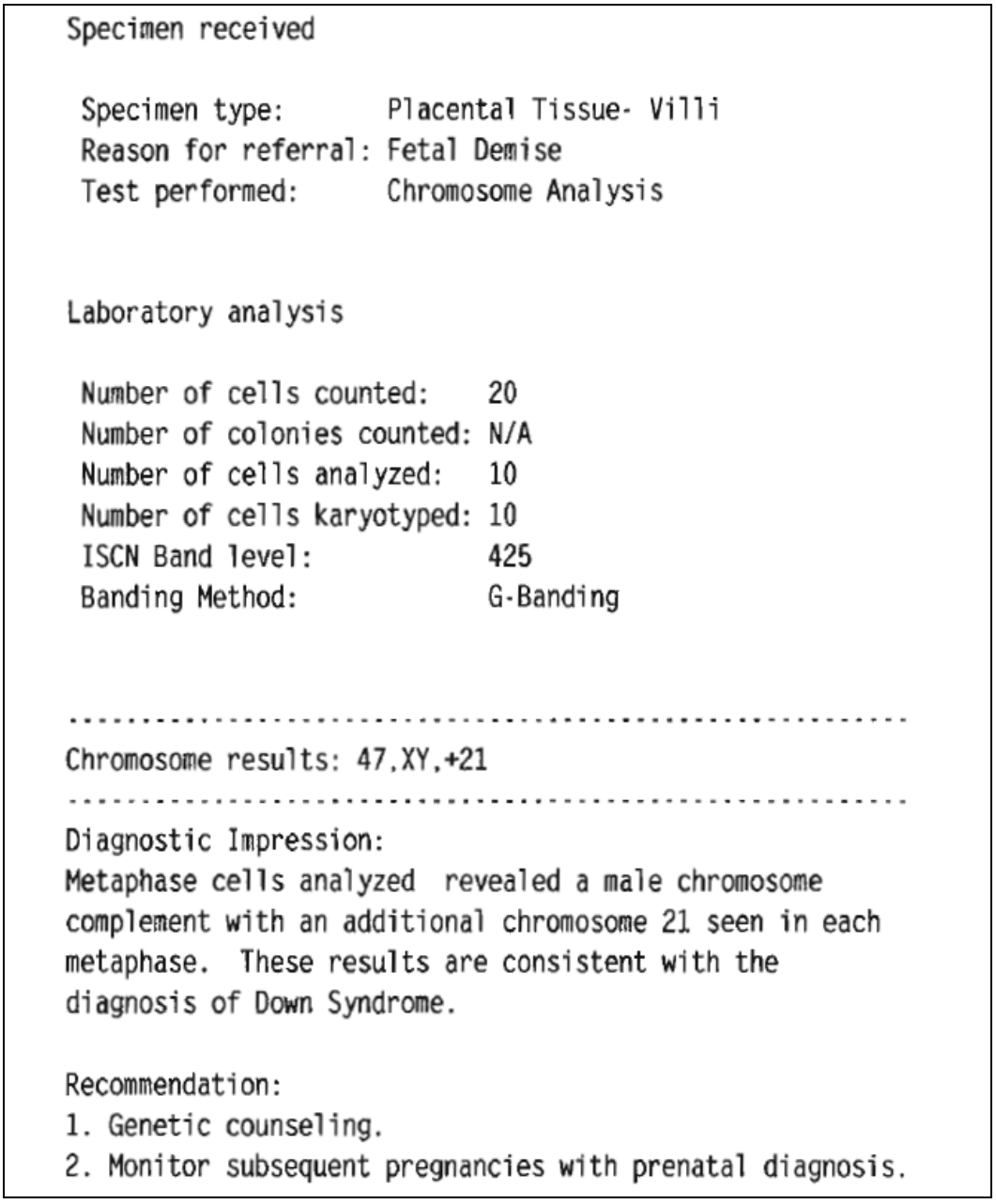
OBX|1|CWE|62357-9^Chromosome analysis result overall interpretation^LN||LA12748-2^Abnormal^LN||||||F|201070201410|||||||||ARUP Laboratories

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 3.5. Sample HL7 version 2 message for chromosome analysis G-banded test result



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 3.6. Partial sample report of chromosome analysis G-banding

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 pan-el^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 pan-el^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 3.7. Sample HL7 version 2 message for chromosome analysis arr copy number change test result

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. Deletion in this region have been reported in multiple pediatric patients with a variety of phenotypes, including

Figure 3.8. Partial sample report of chromosome analysis arr copy number change

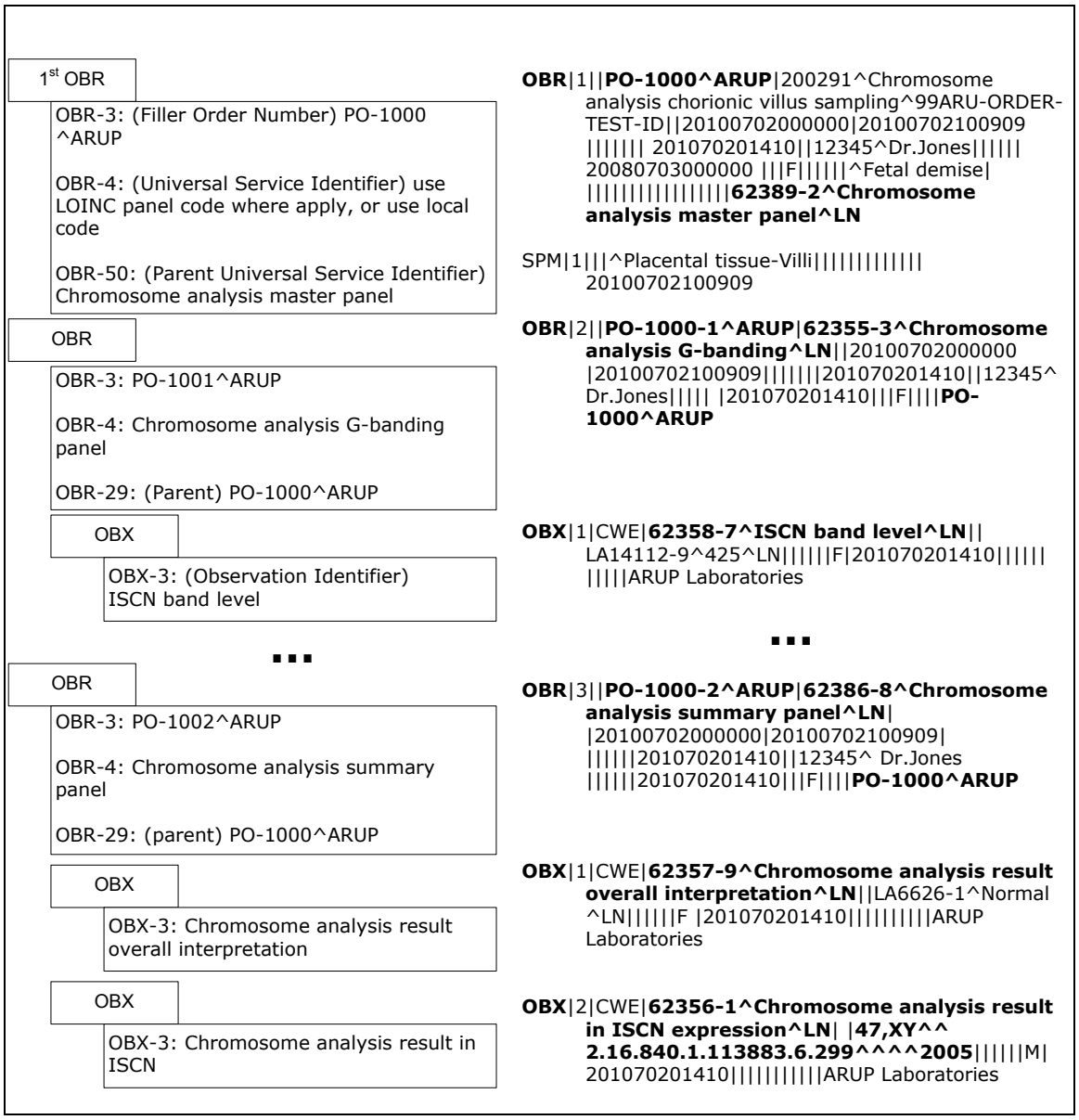


Figure 3.9. Nested HL7 version 2 OBR/OBX segments with Cytogenetic LOINC codes

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CHAPTER 5

LOINC PANELS COUPLED WITH HL7 VERSION 2 MESSAGING STANDARDS FOR TRANSMITTING CYTOGENETIC TEST RESULTS

Introduction

Personalized medicine is changing today's healthcare; it will continue to revolutionize future medicine. Genetic testing is a key component of personalized medicine. The Genetics Test Registry defines a genetic test as the analysis of DNA, RNA, chromosomes, proteins, or metabolites to detect genotypes, mutations, chromosomal changes, or levels of gene expression in a human sample [1]. Genetic testing can help physicians better understand a patient's genetic makeup resulting in more informed clinical decisions about prevention, diagnosis, and disease treatment for improved outcomes [2]. However, many physicians lack the knowledge required to take advantage of the advances brought by the growing scientific understanding of the links between genetics and the predisposition to diseases [3,4]. To take full advantage of information generated by genetic tests in daily patient care, we need to first integrate genetic and genomic data into Electronic Health Records (EHRs) in a consistent coded and structured format.

EHRs can improve caregivers' decisions and patients' outcomes [5]; they are believed to be the catalyst that will allow for the systematic integration of genomic data

within an individual's medical record [6]. One of the most significant benefits of EHRs is their ability to provide clinical decision support (CDS) and education at the point of care. The need for a robust health information technology infrastructure, which includes a CDS component, is critical to realize the promise of personalized medicine [7–9]. Kawamoto et al identified a list of required infrastructure components that must be met to provide CDS for enabling widespread and effective practice of personalized medicine [10]. Standardized data representation—both information models and terminologies—is a vital component among these prerequisites. These standardized detailed clinical models coupled with standardized terminologies can be utilized with messaging standards, which is crucial to allow data flowing electronically from genetic testing laboratories to clinical institutions to be integrated with clinical data in a coded and structured format consistently.

A detailed clinical model is a conceptual specification of the semantics of discrete structured clinical information [11]. The model defines data elements, attributes, relationships, and constraints that are needed to unambiguously and consistently communicate a specific set of clinical data or knowledge. Detailed clinical models are fundamental to achieving semantic interoperability. Briefly, all detailed clinical models can be modeled under the basic name-value pair (also known as entity-attribute-value) paradigm for flexible representation. The structure of a detailed clinical model will specify exactly how standard terminologies are to be used in the model. Each variable within a detailed clinical model is bound to a formal data type to indicate whether it is coded, numeric, or other types of value.

Because detailed clinical models are abstract representations, they should be modeled with a disregard for what technology will be used. Several notable logical representation formalisms have evolved over the years within the medical informatics community. openEHR Foundation has developed archetypes. Archetypes are described using Archetype Definition Language (ADL), which resembles a programming language with its own defined syntax [12]. Intermountain Healthcare has a long history of developing and implementing clinical information models. Information models at Intermountain were first represented using ASN.1 [13]. Intermountain Healthcare has since evolved its ASN.1 models and developed Clinical Element Models (CEMs) [14]. The second generation of models used Clinical Element Modeling Language (CEML), which is based on Extensible Markup Language (XML) to specify CEMs. The most recent version of CEMs is represented using the Constraint Definition Language (CDL), which is a context-free grammar developed by GE Healthcare. Health Level Seven (HL7) has taken the approach of defining HL7 templates, for example, entry-level templates for Clinical Document Architecture (CDA). An HL7 template is a set of constraints on the HL7 Reference Information Model (RIM) or constraints on a RIM derived model such as CDA; it is also expressed in XML. The Unified Modeling Language (UML) has also been used in creating clinical models for EHR systems such as VistA. Archetypes, CEMs, CDA templates, and UML are just a few examples of different formal syntaxes that can be used to represent clinical information models. Logical Observation Identifiers Names and Codes (LOINC) also has a well-developed model for defining data models for complex clinical information; this is through the representation of variables, answer lists and collections that contain them [15].

Guided by the conceptual models, we have developed a set of LOINC terms for reporting constitutional cytogenetic test results. These LOINC panel codes are now available to the public as part of the official LOINC database release. One of the goals of LOINC is to facilitate interoperable exchange of results. We have coupled the cytogenetic LOINC panels with HL7 version 2 results messages to transmit cytogenetic test results from genetic testing laboratories to receiving clinical institutions. The purpose is so that the cytogenetic results can then be embedded in the EHRs as coded and structured data. In this article, we describe the advantages of coupling the LOINC panel content to HL7 V2.x messages, and why we think this approach could be a practical and efficient way for implementers to develop interfaces that utilize standard information models bound to standard terminologies. This strategy could bring not only cytogenetic test results but other types of genetic and genomic data into EHRs.

Background

HL7 version 2.x ("x" could be any version within the version 2 family) messaging standards are the most widely implemented healthcare information standard in the world [16]. Over 95% of U.S. healthcare organizations use HL7 2.x. More than 35 countries have HL7 2.x implementations. HL7 2.5.1 is the Meaningful Use standard for submission of lab results to public health agencies that is published by the Office of the National Coordinator (ONC) for Health Information Technology (HIT) [17]. LOINC is designed to provide universal codes for identifying observations sent in messages in data exchange standards like HL7 and Digital Imaging and Communication in Medicine (DICOM) [18]. Each LOINC term consists of a six-part structure: component (analyte), kind of property, time aspect (timing), system (sample), type of scale, and type of method. The concept of

panels has long existed in LOINC. Within LOINC, panels mean collections that have enumerated discrete contents. In recent years, LOINC has focused on development of panels to represent structured collections of observations [15]. Since LOINC's first release in 1996, it has become the most widely adopted standard for laboratory test result names in the United States and internationally. LOINC is also the Meaningful Use vocabulary standard for laboratory results [17].

Realizing that gaps exist in traditional healthcare information standards for the genetic testing domain, LOINC has been extending its coverage for genetic testing, including cytogenetic testing, in recent years [19,20]. Cytogenetic tests evaluate chromosomes from the nucleus of the cell for changes in number or structure. Cytogenetic testing traditionally has been the first tier of genetic testing for a number of clinical situations such as assessment of a developmentally delayed child, evaluation of a cancerous tumor, or amniocentesis to detect chromosomal anomalies in a fetus [21]. A constitutional cytogenetic abnormality occurs in the germline, while a cancerous cytogenetic abnormality is an acquired (somatic) genetic change associated with a neoplastic process. Cytogenetic testing techniques have evolved over the years. The spectrum of tests spans from conventional banding to molecular cytogenetics where techniques such as flurorescence in situ hybridization (FISH) and cytogenomic microarray (arr) are used routinely. Cytogenetic tests are now playing a more important role in routine patient care by providing the capability of detecting genome wide abnormalities at high resolution. It is essential to develop standard terminologies for representing cytogenetic test results, which will help clinicians to utilize these test results more effectively during their daily practice.

Different from other genetic tests, results of cytogenetic tests are reported using the International System for Human Cytogenetic Nomenclature (ISCN). ISCN was created by the International Standing Committee on Human Cytogenetic Nomenclature, which has been a gold standard of describing cytogenetic and molecular cytogenetic findings in both clinical and research reports since 1960 [22]. ISCN provides a list of symbols and abbreviated terms in adjunct with a set of rules to annotate cytogenetic test outcomes: symbols such as *p* for short arm of chromosome, *q* for long arm of chromosome, *del* for deletion, *ish* for in situ hybridization, *arr* for microgenomic microarray, and plus sign (+) for gain. As the field of cytogenetics continues to include several molecular-based technologies, the latest revision of ISCN was published in 2009 to provide more up to date and accurate descriptions of the new technologies, e.g., a new chapter was added with nomenclature examples describing copy number detection due to rapid advancement in microarray technology [23]. ISCN is expected to continuously evolve as molecular technologies improve.

Methods

Each LOINC term corresponds to a single test result or panel. LOINC panels are collections that have enumerated discrete contents. The LOINC panel approach has been traditionally used for reporting laboratory collections such as a complete blood count (CBC) panel and a CHEM-7 panel. In recent years, LOINC panels have been successfully applied to patient assessments for clinical LOINC, where a nested panel structure is used to represent the hierarchical nature of the survey instrument and questionnaires. Panel specific attributes and structured answer lists have been evolved to better support

LOINC panels; LOINC panels are now a robust semantic data model through years of iterative refinement. [24]

In the genetics and genomics domain, LOINC panels have also been successfully used to represent genetic variation results [19]. This has led to the first cross-country transmission of coded and structured genetic test results in 2009 [25]. We have followed a similar approach for genetic variation to represent cytogenetic test results. In the genetic variation model, detailed clinical models were developed first to clearly represent the semantic relationships of data elements contained in result reports of sequencing and genotyping based genetic tests, where identified DNA sequence variants are located within a gene. These conceptual information models are structured collections of enumerated discrete data elements contained in a genetic variation test result report, which are used to guide the creation of LOINC codes. Each data element slot in the information models has its corresponding LOINC code. The hierarchical relationship is represented using LOINC panel codes that are linked to an enumerated set of child elements. The child LOINC codes themselves can be panel codes, which enable multiple levels of nesting if needed. A LOINC panel code can have panel-specific attributes, e.g., it allows cardinality to be specified for each child element. If the data element has a coded result, the value of the result can be drawn from a LOINC answer list, or if applicable, from other standard terminologies such as SNOMED-CT for diseases, and Human Gene Nomenclature Committee (HGNC) for gene symbols and identifiers.

An HL7 2.x Unsolicited Point-In-Care Observation without Existing Order (ORU) message definition allows nesting of Observation Request segments (OBRs). Each OBR segment may contain one or many Observation Result segments (OBXs).

LOINC codes were initially designed to provide universal codes in messages, specifically to be used in OBR-4 Universal Service Identifier field and OBX-3 Observation Identifier field in an HL7 2.x message. The hierarchical LOINC panel structure fits nicely with the nested structure of OBR and OBX segments: the LOINC panel code will be sent in the OBR-3 field, the enumerated set of child LOINC terms that are contained in a panel will be sent in the OBX-5 fields as appropriate. If a LOINC panel contains nested panels, then nested OBRs will be used.

The LOINC panel modeling approach used for developing the genetic variation model started from conceptual representation based on the business requirements and is not constrained by any particular representation formalism. It was developed though with a specific technology in mind, in this case, to transmit genetic variation results through HL7 2.x messages, the most widely implemented and most commonly used messaging method in the U.S. To help implementers, detailed instructions and guidance of how to use this LOINC-HL7 messaging framework for reporting genetic variations, where LOINC panels are tightly coupled with HL7 2.x messages, are described in the HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model, Release 1 [19].

Results

Applying the same LOINC panel approach to develop LOINC codes for cytogenetic test results worked nicely. We have created the LOINC panel, “Chromosome analysis master panel in Blood or Tissue” (LOINC # 62389-2), as an overall parent. This master panel contains three subpanels, which define the results of a G-Band, FISH and arr study, respectively. All cytogenetic test results are represented using ISCN notation, but

for tests that were done with different techniques, discrete data that were sent along with the result report varies, therefore, a different panel was created. The master panel for cytogenetic test results contains 65 LOINC codes, 7 of which are panel codes. We have reused the LOINC codes from the genetic variation model as much as possible. In this article, we will not describe the cytogenetic LOINC panels in details, since the complete list of the cytogenetic panels and their enumerated LOINC terms can be obtained from the LOINC database. One can use the freely available RELM A tool from Regenstrief Institute or through the online search tool through the LOINC website to search and view the complete panel hierarchy [26].

We have also developed the HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Cytogenetics Model, Release 1 [27]. This implementation guide was sponsored by the HL7 Clinical Genomics Workgroup, the same group that sponsored the genetic variation model. The implementation guide specifies in details how the LOINC panels for cytogenetics should be used with HL7 OBR and OBX segments with sample messages for illustrations. The implementation guide was balloted as an HL7 informative document in the January 2012 HL7 ballot. Representatives that voted on the implementation guide came from government/non-profit organizations, pharmaceutical companies, health care provider organizations, and vendors.

Discussion

Genetic testing is increasingly relevant to mainstream medicine since the successful completion of the Human Genome Project in April 2003. A genetic test can provide information on predispositions for a disease, presence of a disease, the risk of passing a disease onto offspring, and potential positive or adverse responses to therapeutic inter-

ventions. More genetic tests are becoming available to clinicians. There are currently about 2,200 genetic tests available for clinical use and the number is continuing to grow rapidly. Patients are being exposed to greater amounts of genetic information routinely, and genetic/genomic data are becoming increasingly important for clinical decision making. A study has shown that clinicians agree that knowing a patient's genetic profile can influence treatment decision-making and importantly, can improve patient outcomes [28].

The Personalized Healthcare Workgroup of the American Health Information Community (AHIC) has identified inclusion of relevant results from genetic tests in the EHR as immediate priorities for recommendation [29]. Government support for HIT has been strong in recent years, especially, under the American Recovery and Reinvestment Act of 2009 (ARRA). The Health Information Technology for Economic and Clinical Health Act (HITECH) offers funding for infrastructure and incentive payments to providers who adopt and use EHRs in a meaningful way. The Secretary's Advisory Committee on Genetics, Health, and Society to the Health Information Technology Policy Committee had urged the committee to represent genetic and genomic information as fundamental information that need to be integrated into EHRs rather than as ad hoc specialty information. It specifically requested that the Meaningful Use objective to "incorporate lab tests into EHR" should explicitly reference genetic/genomic test results [30]. As the HIT infrastructure in the US improves and Meaningful Use of EHRs continues to expand in the near future, it is important to continue developing infrastructure components that are critical to successful and widespread clinical integration of genetic and genomic data, hence to promote the continued development of personalized medicine.

Advantages of the LOINC Panel Approach

Broad use of EHRs with coded and structured data is essential for realizing the promise of personalized medicine. Demand for standardized representation of genetic test results will continue to rise. The LOINC panel approach offers several advantages in meeting the needs in this particular area.

First, the LOINC panel approach uses a well-developed model for representing a collection of clinical observations. LOINC panels have proven to be robust, flexible, and sustainable; they are not only able to represent test results in the genetics domain as demonstrated by the genetic variation model and the cytogenetics model, but also in other domains such as representing survey instruments and questionnaires. The LOINC panel approach continues to be applied in exciting new areas, for example, the Phenotypes and eXposures (PhenX) project, which develops measures for genome-wide association and other types of studies [31]. LOINC panels are model driven; they provide the agility and flexibility that is crucial to support the rapidly evolving nature of the genetic testing field. As existing technologies evolve, new technologies emerge, and as new findings are discovered and need to be included in the clinical reports, LOINC panels can be easily adapted to the changes and new additions. The LOINC panels we have created for the cytogenetic test results are currently limited to constitutional cytogenetic tests, but we believe we could extend these panels to cover the reporting needs for cancer cytogenetic tests. Array technology is rapidly being incorporated into cytogenetics and molecular genetics laboratories; cytogenetics is increasingly expanding into cytogenomics. When we developed these LOINC panels, single-nucleotide polymorphism (SNP) microarrays were only used in a research setting but are now routinely used by many clinical laboratories.

Our panels are versatile enough to easily incorporate results from these platforms. This could be another exciting new test for us to cover in the near future by extending the LOINC cytogenetics panels. As the HL7 2.5.1 implementation guide for reporting cytogenetic tests reaches broader audiences and different stakeholders, we expect to continue refining these LOINC panels based on ballot feedback through the rigorous HL7 ballot reconciliation process.

Second, by design the natural coupling between LOINC panels and the HL7 2.x messages will allow EHR systems to leverage their existing infrastructure especially in the U.S. realm. We expect this will lead to rapid implementation and development for supporting new standardized and coded data structures for genetic test results where LOINC panels and HL7 v.2 messages are used. Both LOINC and HL7 v.2 messaging standards are widely implemented in the U.S.; Meaningful Use will only make them even more accessible to institutions and clinics. Collaborating with the Harvard Medical School – Partners Healthcare Center for Personalized Genetic Medicine, Intermountain Healthcare reported the first cross-country transmission of coded and structured genetic test results. This pilot implementation was based on the existing HIT infrastructure of Intermountain Healthcare, and conforms to the HL7 2.5.1 implementation guide for genetic variation model. The same implementation strategy could easily be reused when Intermountain Healthcare implements the cytogenetics model. The pilot implementation's success has demonstrated that using the LOINC panel approach to represent genetic test results would require few changes by implementers, which is significant considering the high volume of genetic and genomic data that EHRs will be expecting to receive in the very near future. The price to consumers to sequence a complete human genome is pre-

dicted to drop to $1000 in 2014[32], and experts believe that we may expect tens of millions of personal genomes to be sequenced worldwide by 2020 [33].

Third, the coupling between LOINC panels and HL7 2.x messages provides a mechanism that could potentially overcome some of the known weaknesses of HL7 2.x messages. HL7 2.x messages are known to have vague definitions of message structures and have built in a substantial amount of optionality, which has left room for a great deal of variability among implementations and has created difficulties for achieving true interoperability. LOINC panels allow semantic relationships to be expressed unambiguously through the LOINC hierarchical structure, which includes cardinalities, data types, and answer lists. LOINC codes are created for each data element contained in a LOINC panel. So LOINC panels are able to provide not only a standard structure for representing a collection of clinical observation, but also standard and widely accepted terminologies for data element names. Without standard terminologies, data models alone will not easily be shared across different systems. Using the LOINC panels to guide the construction of a HL7 2.x message creates synergy by combining the well-developed LOINC model for defining semantics and widely implemented HL7 2.x messages as the messaging vehicle.

Fourth, LOINC panels as one form of physical representation can be transformed to other information modeling formalisms to meet different implementation technology requirements. The Implementation Guide for CDA Release 2 Genetic Testing Report uses LOINC codes for genetic variations and cytogenetics in defining its genetic variation and cytogenetics sections [34]. During the genetic variation model pilot implementation, Intermountain Healthcare transformed the LOINC panels for genetic variations to ASN.1 models and used the latter as storage models for storing genetic variation test results in

the Clinical Data Repository. In contrast with HL7 templates and CDA templates, LOINC panels use business names, which align more closely to the detailed clinical models. Creation of LOINC panels does not require the same kind of steep and long learning curve that implementers experienced in creation of HL7 and CDA templates. Domain subject experts could focus on accurately expressing the clinical concept and knowledge that they need to model to meet the business requirements and vet the LOINC panels, rather than having to learn and struggling with how to express them through complex physical representation within specific modeling formalism limitations. This advantage could be important while we are trying to bridge the knowledge gap due to the lack of genetic and genomic knowledge among clinicians and most likely even more so among healthcare IT professionals in general. The HL7 Structured Document Workgroup has introduced the "greenCDA" technology that aims to simplify CDA creation and implementation while maintaining the common basis required for semantic interoperability [35]. "greenCDA" uses simplified XML schemas and business names. Though the "greenCDA" technology is promising, it has potential issues as well. For example, it is currently still a very manual process and yet to be automated, widely accepted, implemented, and tested. On the other hand, LOINC panels have been widely implemented and tested in many domains including genetic testing.

Challenges

We have encountered some challenges with the LOINC panel approach through our development of cytogenetics LOINC panels. We found it is sometimes challenging to determine when a LOINC term used in a panel should be reused in other panels and when a new LOINC term or panel should be created. When a LOINC term is used to represent

a data element within a panel, we need to evaluate it in the context of that panel to make a determination. When we create LOINC panels and their contained discrete LOINC codes, we might need to take into consideration that a particular term could be potentially reused by other panels, and therefore not to constrain its LOINC six-axis for a narrower use case only. For example, we did not constrain the method part of the LOINC term 62366-0, *Recommendation:Imp:Pt:Patient:Doc*, to Molgen (molecular genetics), so this term could be reused in other domains other than genetics.

A LOINC term with a defined answer list may add more complexity to the sharing and reuse of existing LOINC codes across different LOINC panels. LOINC allows answer lists to be declared as either normative or example. An answer list that is normative is meant to be comprehensive of all allowed values and adheres to a published standard, while an example answer list only displays some example answers to the question posed by the LOINC code. LOINC answer lists can contain enumerated values that are stored in the LOINC database, or the answer list can "point" to an external list of values drawn from another code system that is uniquely identified by an Object Identifier (OID). A LOINC code that may seem appropriate for reuse might have a different answer list with different meanings in the context of two different LOINC panels. It will be a continuous and iterative effort for LOINC to address and harmonize these use cases. Interoperability is a journey, and developing standardized information models coupled with standard terminologies—one of the most fundamental components of interoperability—is a journey itself. The LOINC Committee is continuously improving and iteratively refining its approach for developing LOINC panels.

Use of LOINC panels is just one form for representation of conceptual information models. Different representation formalisms exist today, each with its own advantages and disadvantages. They have each been implemented differently, which in a way has become a significant barrier to interoperability itself. To solve this particular problem, the Clinical Information Modeling Initiative (CIMI), an international collaboration, is attempting to provide a universally acceptable representation formalism for modeling health information content [36]. It is our hope that models derived from universally vetted detailed clinical models bound to LOINC codes could be transformed into different representation formalisms such as HL7, CDA templates, and archetypes and be implemented in different implementation technology environments.

Clinical Decision Support

Standard representation of genetic and genomic data is a vital component of the CDS infrastructure for personalized medicine. Genetic and genomic discovery is taking place at a breathtaking pace since the completion of the Human Genome project, and it has added a new dimension to the idea that "clinicians need help" that triggered the beginning of medical informatics decades ago. Clinicians will be unable to keep track of the genetic and genomic information relevant to patient care, especially trying to interpret it in the context of an individual patient. CDS rules for genetic and genomic information that are incorporated in EHRs have the potential to prevent harm to patients due to misinterpretation of genetic test results and help clinicians provide adequate and appropriate counseling. To maximize such potential, genetic and genomic data must be integrated into EHRs as coded and structured data represented using accepted standards. Decision support must be delivered as part of the clinician's decision-making process at the appro-

priate time, and EHRs must be flexible to meet the rapidly growing and evolving nature of genetic and genomic information and the field of genetic testing.

Integration of coded and structured genetic and genomic data within EHRs has also made it possible for the secondary use of the combination of genetic, genomic, and clinical data. The Electronic Medical Records and Genomics (eMERGE) Network is a pilot project that is funded by the National Human Genome Research Institute and the National Institute of General Medical Sciences [37]. eMERGE participants have been exploring whether the use of EHRs could support genome-wide association analysis.

Conclusions

LOINC panels provide structured semantic representation for a list of discrete clinical data elements, as well as binding to widely accepted standard terminologies for naming the collections and the individual data elements they contain. LOINC panels also provide the agility and flexibility that are crucial to meet the integration requirements of the dynamic and rapidly growing field of genetic testing. Coupled with HL7 2.x messages, the most widely implemented HIT standard in the world, LOINC panels can lead to rapid implementation by leveraging existing EHR infrastructures especially in the U.S. realm.

LOINC panels were previously used in the development of LOINC terms for genetic variation test results. We have successfully applied the same LOINC panel approach to develop LOINC terms for cytogenetic test results, which has further proven that LOINC panels can be an effective modeling formalism for representing genetic tests results in the general case. Implementers can also potentially transform LOINC panels into other modeling formats to fit different implementation technology requirements.

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CHAPTER 6

DISCUSSION

Summary

Genetic and genomic information needs to be integrated into EHRs in a coded and structured format to be clinically meaningful and to enable clinical decision support at the point of care. However, today's EHRs are not ready for genomic medicine [1]. Lack of standardized data representation and terminology standards are among major barriers for interoperable integration of genetic and genomic test information. Among different types of genetic tests, cytogenetics is often the first tier of genetic testing for assessment of a child with multiple congenital abnormalities and/or developmental delay, prenatal detection of chromosome anomalies, detection of mosaicism, or evaluation of oncological specimens [2]. Currently, most genetic test results, including cytogenetic test findings, are stored in long textual reports. These reports are then transmitted from the testing laboratories to the clinical institutions and stored as narrative texts.

During this study, we first evaluated LOINC, the de facto terminology standard for representing laboratory test names and results. We found that a gap existed in LOINC to support the integration of cytogenetic test results into EHRs. There were only a few LOINC terms for cytogenetics and they do not match well with how cytogenetic tests are reported. To fill this gap, we have taken the LOINC panel approach and developed

LOINC panels and terms for representing constitutional cytogenetic test findings by analyzing sample clinical reports.

We contacted five large cytogenetics laboratories in the U.S.: ARUP Laboratories, Mayo Clinic Cytogenetics Laboratory, Emory Cytogenetics Laboratory, Genzyme Genetics (now Integrated Genetics, LabCorp Specialty Testing Group), and Signature Genomics. Three of the five laboratories were able to send us their sample reports. We received 19 sample reports from ARUP, 12 from Emory, and 16 from Mayo Clinic. We created information models based on the key data elements extracted from the ARUP result reports. The information models were able to cover the key data elements extracted from the Mayo result reports. But the Emory result reports for cytogenomic microarray analysis contained a "microarray platform version number," which did not exist in both ARUP and Mayo reports. We believe this new data element is important and should be included in our information models. Based on the information models, we created a master panel to contain three LOINC subpanels; each of the three subpanels held the structure for chromosome analysis results that uses a different technique: G-banding, FISH, and cytogenomic microarray.

Our research goal was to cover the most important data elements contained in the reports. We believe the list of key data elements that we extracted from these three cytogenetic laboratories covered about 80% of the data variable names in the cytogenetic test result report, and the LOINC panels we created are able to represent 100% of these key data elements. We then created an HL7 implementation guide using the LOINC panel codes. The strategy for using LOINC panels to define the contents of data exchange mes-

sages represents a pattern that can be used for other types of genetic results as well as for the representation of other non-genetic complex data.

Contribution to Biomedical Informatics

The Secretary's Advisory Committee on Genetics, Health, and Society stated to the Health Information Technology Policy Committee that "*Clinical decision support for genetic/genomic information in the context of the EHR has the power to prevent potential harms to patients due to misinterpretation of genetic test results and help primary care physicians provide adequate and appropriate counseling. Clinical decision support tools, made available at appropriate times, will enhance patient care. This goal cannot be met unless genetic/genomic information is available in the EHR.*" [3]. By focusing on developing standardized data representation for cytogenetic test result reports, this study has helped to overcome one of the main barriers for integrating genetic/genomic information into EHRs and enabling clinical decision support.

The results of this study filled the gap that previously existed: there were no standard information models and no standard terminologies for representing constitutional cytogenetic test results. LOINC is the de facto terminology standard for laboratory results. LOINC panels and LOINC terms for constitutional cytogenetic test results are now contained in the LOINC database openly accessible by the public.

This study further supported that the use of the LOINC panel approach coupled with HL7 V2 messaging standards could be a practical and efficient way to develop interfaces that utilize standard information models and standard terminologies; an HL7 V2 implementation guide for cytogenetic test results was balloted as a result. This generic LOINC panel approach can be applied not only to cytogenetic test results, but potentially

also to other types of genetic test results. It takes advantages of existing infrastructure in almost all EHR systems in the current US market, which will certainly help to speed up the adoption and implementation process, and thus, help to make structured and coded genetic/genomic information available in the EHR in the very near future.

Future Directions

Personalized medicine is experiencing a rapid growth following the completion of the human genome project. The consumer price to sequence a complete human genome is predicted to drop to $1000 in 2014 [4]. Experts also believe that we may expect tens of millions of personal genomes to be sequenced worldwide by 2020 [5]. This is an exciting time for the biomedical informatics community to build foundations necessary to bridge the chasm between the bench and the bedside to take full advantage of the promise of personalized medicine. Ample opportunities exist to expand and refine our study.

This study focused on constitutional cytogenetic test results. We intend to analyze cancer cytogenetic test reports to expand our information models and LOINC panels. As new technologies, such as single-nucleotide polymorphism (SNP) arrays, now allow for clinical applications, we plan to expand the LOINC coverage to include SNP arrays. SNPs are DNA sequence variations in which a single nucleotide in the sequence of the genome differs between individuals or between paired chromosomes in an individual [6]. As we expand the content to cover SNP arrays and cancer cytogenetic test results, we will continue to ballot the implementation guide through HL7 in the future under the support of HL7 Clinical Genomics Workgroup. However, for the current cytogenetics HL7 implementation guide [7], we feel that it is more important at this stage to start actively exploring the opportunities of creating a pilot real-world implementation. Real-world im-

plementations prove the standard is implementable and support real-world conditions. A pilot real-world implementation will provide us valuable information to further refine and improve the standard.

Cytogenetic test results are expressed using ISCN notations. Currently, though we have assigned this data element a coded data type, we expect the result will be stored as a string initially. A parser that can parse the ISCN expression based on the latest 2009 version of the nomenclature could potentially be an extremely valuable tool. It can dissect the cytogenetic findings based on the nomenclature and store the complete finding as discrete structured results. During this study, we did not focus on structuring the narrative texts within the recommendation and diagnostic impression sections. We believe that the best approach to interoperability is taking incremental steps; therefore, our goal in this study was to get the key information of constitutional cytogenetic test results into EHRs as coded and structured format first. We could apply natural language processing in the future to extract key information from narrative texts as the need arises.

Once coded and structured cytogenetic test results are integrated into the EHRs, it will lead to many exciting opportunities. We hope to study how to best display the cytogenetics clinical report in a clinician friendly format. We also hope to use alerts to bring available best practice treatment guidelines of syndromes to the attention of clinicians, and to use infobutton technology to present the most relevant genetics information to the clinicians that are tailored based on the cytogenetic test results of an individual patient. We would also like to conduct secondary use studies on the integrated cytogenetic and phenotypic data.

Unlike basic clinical chemistry tests and simple imaging studies where results represent a clinical picture at a single point in time, genetic tests results on tissues derived from the germline, such as constitutional cytogenetic tests, are valid for the lifetime of the individual, and perhaps longer as genetic data may have relevance for the individual's offspring and other relatives [8]. However, current interpretation of genetic test findings for complex conditions may change over the course of an individual's lifetime as a result of new research findings or advances in technology to interpret extensive sets of genomic data. We plan to explore the strategies of how to access an up-to-date genetic knowledge base, how to trigger and prompt for reinterpretation of the original test results (when relevant new knowledge emerges or updates to the knowledge base have been made that require previous interpretations to be revisited) and how to notify clinicians and patients in an efficient and meaningful way.

Finally, we expect to expand beyond the cytogenetic testing domain in the future. It is now time to start bridging the efforts of both the bioinformatics and medical informatics worlds to integrate genetic and genomic information with EHRs. It will be important for us to work with the genetic experts and clinicians to understand the degree of complexity we need to bring genetic and genomic data into EHRs to be the most effective. As the genetic and genomic information flow from the laboratory bench to the bed side, different users may have different requirements regarding the level of complexity they would like to receive while maintaining data traceability during the entire data flow. It will also be important for us to leverage existing standards, tools, and expertise from the bioinformatics and medical informatics communities to provide best patient care. For example, bioinformatics researchers have started the Sequence Ontology (SO) project for

the purpose of standardizing genomic annotation. Sequence ontology is a structured controlled vocabulary for the parts of a genomic annotation [9]. The Genome Variation Format (GVF) is a computable standard variation file format for human genome sequences that uses the sequence ontology as descriptive terms [10]. We hope to work with the SO and GVF experts to see how we could use standard terminologies such as LOINC and HL7 messaging standards to help transmit variant files with EHR suitable information from the testing laboratories and embedding them in the EHRs, and improve the existing HL7 genetic variation implementation guide.

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APPENDIX

LOINC CYTOGENETICS PANEL HIERARCHY

LOINC#	LOINC Name	Cardinality	Data Type
62389-2	Chromosome analysis master panel in Blood or Tissue		
62386-8	Chromosome analysis summary panel in Blood or Tissue by Molecular genetics method	1..1	
62356-1	Chromosome analysis result in ISCN expression in Blood or Tissue by Molecular genetics method	1..1	
62357-9	Chromosome analysis overall interpretation [interpretation] in Blood or Tissue Qualitative by Molecular genetics method	1..1	
48002-0	Genomic source class [Type] in Blood or Tissue by Molecular genetics method	1..1	CWE
51967-8	Genetic disease assessed [Identifier] in Blood or Tissue by Molecular genetics method	0..n	CWE
51969-4	Genetic analysis summary report in Blood or Tissue Document by Molecular genetics method	0..1	FT
62355-3	Chromosome analysis panel in Blood or Tissue by Banding		
62386-8	Chromosome analysis summary panel in Blood or Tissue by Molecular genetics method	1..1	
62356-1	Chromosome analysis result in ISCN expression in Blood or Tissue by Molecular genetics method	1..1	
62357-9	Chromosome analysis overall interpretation [interpretation] in Blood or Tissue Qualitative by Molecular genetics method	1..1	
48002-0	Genomic source class [Type] in Blood or Tissue by Molecular genetics method	1..1	CWE
51967-8	Genetic disease assessed [Identifier] in Blood or Tissue by Molecular genetics method	0..n	CWE

51969-4	Genetic analysis summary report in Blood or Tissue Document by Molecular genetics method	0..1	FT
62358-7	ISCN band level [#] in Blood or Tissue Qualitative by Molecular genetics method	1..1	
62359-5	Chromosome banding method [Type] in Blood or Tissue by Molecular genetics method	1..1	
62360-3	Cells analyzed [#] in Blood or Tissue by Molecular genetics method	0..1	
62361-1	Cells counted [#] in Blood or Tissue by Molecular genetics method	0..1	
55199-4	Cells karyotyped.total [#] in Blood or Tissue	0..1	
62362-9	Colonies counted [#] in Blood or Tissue by Molecular genetics method	0..1	
62363-7	Mosaicism detected in Blood or Tissue by Molecular genetics method	0..1	
62364-5	Test performance information in Unspecified specimen Narrative	0..1	
62365-2	Diagnostic impression [interpretation] in Unspecified specimen by Molecular genetics method Narrative	0..1	
62385-0	Recommendation [interpretation] Document	0..1	
62366-0	Recommended action [Identifier]	0..n	
62367-8	Chromosome analysis panel in Blood or Tissue by Fluorescent in situ hybridization (FISH)		
62386-8	Chromosome analysis summary panel in Blood or Tissue by Molecular genetics method	1..1	
62356-1	Chromosome analysis result in ISCN expression in Blood or Tissue by Molecular genetics method	1..1	
62357-9	Chromosome analysis overall interpretation [interpretation] in Blood or Tissue Qualitative by Molecular genetics method	1..1	
48002-0	Genomic source class [Type] in Blood or Tissue by Molecular genetics method	1..1	CWE
51967-8	Genetic disease assessed [Identifier] in Blood or Tissue by Molecular genetics method	0..n	CWE
51969-4	Genetic analysis summary report in Blood or Tissue Document by Molecular genetics method	0..1	FT
62368-6	Cell phase [Type] in Blood or Tissue by Molecular genetics method	0..1	
62369-4	FISH probe name panel in Blood or Tissue by Molecular genetics method	0..n	
62370-2	FISH probe gene name [Identifier] in Blood or Tis-	0..1	

	sue by Molecular genetics method		
62371-0	FISH probe locus [Identifier] in Blood or Tissue by Molecular genetics method	0..1	
62372-8	FISH probe vendor [Identifier] in Blood or Tissue by Molecular genetics method	0..1	
62360-3	Cells analyzed [#] in Blood or Tissue by Molecular genetics method	0..1	
62364-5	Test performance information in Unspecified specimen Narrative	0..1	
62365-2	Diagnostic impression [interpretation] in Unspecified specimen by Molecular genetics method Narrative	0..1	
62385-0	Recommendation [interpretation] Document	0..1	
62366-0	Recommended action [Identifier]	0..n	
62343-9	Chromosome analysis microarray copy number change panel in Blood or Tissue by arrCGH		
62386-8	Chromosome analysis summary panel in Blood or Tissue by Molecular genetics method	1..1	
62356-1	Chromosome analysis result in ISCN expression in Blood or Tissue by Molecular genetics method	1..1	
62357-9	Chromosome analysis overall interpretation [interpretation] in Blood or Tissue Qualitative by Molecular genetics method	1..1	
48002-0	Genomic source class [Type] in Blood or Tissue by Molecular genetics method	1..1	CWE
51967-8	Genetic disease assessed [Identifier] in Blood or Tissue by Molecular genetics method	0..n	CWE
51969-4	Genetic analysis summary report in Blood or Tissue Document by Molecular genetics method	0..1	FT
62373-6	Human reference assembly release, UCSC version [Identifier] in Blood or Tissue	0..1	
62374-4	Human reference sequence assembly release number in Blood or Tissue by Molecular genetics method	1..1	
62375-1	Microarray platform [Identifier] in Blood or Tissue by Molecular genetics method Narrative	1..1	
62376-9	Microarray platform version number in Blood or Tissue by Molecular genetics method Narrative	1..1	
62377-7	Chromosome copy number change panel in Blood or Tissue by Molecular genetics method	0..n	
62378-5	Chromosome copy number change [Type] in Blood or Tissue by Molecular genetics method	0..1	
62379-3	Chromosome band involved start in Blood or Tissue	0..1	

	by Molecular genetics method	
62380-1	Chromosome band involved end in Blood or Tissue by Molecular genetics method	0..1
62381-9	Base pair start coordinate [#] in Blood or Tissue by Molecular genetics method	0..1
62382-7	Base pair end coordinate [#] in Blood or Tissue by Molecular genetics method	0..1
62383-5	Flanking normal region before start in Blood or Tissue by Molecular genetics method	0..1
62384-3	Flanking normal region after end in Blood or Tissue by Molecular genetics method	0..1
62364-5	Test performance information in Unspecified specimen Narrative	0..1
62365-2	Diagnostic impression [interpretation] in Unspecified specimen by Molecular genetics method Narrative	0..1
62385-0	Recommendation [interpretation] Document	0..1
62366-0	Recommended action [Identifier]	0..n