Using LOINC and HL7 to Standardize Hemoglobinopathy Screening Result Reporting

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Introduction

Hemoglobinopathy screening is an integral part of newborn screening (NBS). It identifies infants with serious hemoglobin (Hb) disorders, such as sickle cell disease, in the first weeks of life. Different NBS programs use different methods for screening as well as different sets of controls, so the Hb types and disorders that can be presumptively identified based on those types are not consistent across labs. Even in cases where two laboratories identify the same Hb, they might not report it in the same way. Our goal was to create a uniform method for electronically reporting NBS hemoglobinopathy results that would encompass the variation across programs. By collaborating with hemoglobin and NBS experts from multiple federal and state agencies, NBS programs, and laboratories, we devised a straightforward method for reporting that relies on reporting individual Hb types.

Background

Universal hemoglobinopathy screening as part of NBS was formally recommended in 1987.[1] This recommendation followed a 1986 study that established penicillin prophylaxis against infection as a treatment that could significantly reduce the incidence of pneumococcal sepsis in patients with sickle cell anemia.[2] Even with this NIH Consensus Recommendation, it took until 2006 for all U.S. newborn screening programs to add universal screening for sickle cell anemia to their screening panel.[3] Because the screening technology provides detection of many other hemoglobins, most programs have included other sickle cell diseases in their screening panels, particularly sickle cell-hemoglobin C disease (Hb SC) and sickle cell- beta thalassemia (Hb S/ßTh). As screening has progressed, over 700 Hb variants have now been identified. Some hemoglobin mutations cause significant disease, while others have minimal, if any, clinical consequences, or the clinical implications are not yet known.[4]

Different NBS programs detect and report different Hb variants. Methodologies used in the screening process include isoelectric focusing (IEF), citrate agar gel electrophoresis, high pressure liquid chromatography (HPLC), mutation analysis, or a combination of these methods. The number of Hb types reported on initial screening depends primarily on the controls available in a particular lab. There are a limited number of commercially available Hb controls, but some screening laboratories may also have local controls for different hemoglobins based on the samples they have analyzed previously. Hemoglobin variant nomenclature evolved over time. Initially, following the naming of normal adult hemoglobin as Hb A and sickle hemoglobin as Hb b, variants were to be named in alphabetical order as discovered. Widespread use of Hb S for sickle[5] and the realization that the number of alphabetical characters was limited soon changed that. Instead, hemoglobin variants came to be named, at least in part, based on the location where they were discovered (e.g. Hb Istanbul and Hb Madrid).[6] Nomenclature including the amino acid substitution and the hemoglobin chain has also been used and a much more sophisticated nomenclature system is currently under development.3

Until now, most NBS labs and/or programs have provided screening results to specimen submitters as paper reports, with variability in the hemoglobins reported and the manner in which they are reported. Hemoglobinopathy results are most commonly reported as a text string with all of the Hb types found in a particular sample listed in descending concentration. For example, an infant with a normal Hb screen who has a hemoglobin consistent with Hb F with a smaller amount of Hb A (compared to known controls) would have a probable screening result of “Hb FA.” On the other hand, if more Hb A than Hb F were observed, which can occur if an infant receives a blood transfusion, the probable result would be reported as “Hb AF.” Probable sickle cell trait would be “Hb FAS” while probable sickle cell anemia would be “Hb FS.” The term “probable” is

usually used to denote that the hemoglobin pattern observed is a screening result consistent with certain controls and a more detailed hemoglobin confirmation has not been performed.

The recent push for electronic health record (EHR) adoption and electronic transmission of lab results provided the opportunity to develop a standard method for electronic reporting of NBS results using nationally-accepted vocabulary and electronic messaging standards, namely LOINC® and HL7®.[7] LOINC (Logical Observation Identifiers Names and Codes) contains standard codes for identifying laboratory tests and other clinical measures, and HL7 (Health Level 7) specifies the standards for electronic health messaging. Early efforts to develop a method for reporting Hb screening results focused on the traditional way of reporting the result as a text string and attempted to assign a separate code to each unique pattern that could be observed as well as its interpretation. However, given that more than 700 Hb variants are known to date, each possible observed Hb in combination with other possible Hb creates an exponential number of strings and codes, which is ultimately unsustainable. Therefore, we have developed another method for reporting Hb screening results as described below.

Methods

Members of multiple agencies, NBS programs and laboratories collaborated as part of a NBS hemoglobinopathy workgroup. Our goal was to develop a straightforward and sustainable method for reporting hemoglobinopathy screening results. The workgroup initially had a face-to-face meeting to discuss issues related to hemoglobinopathy screening across NBS programs, including the variability in nomenclature, screening methodology and results reporting; this meeting was followed by multiple phone meetings.

Our first task was to create a reporting method that complied with current HL7 messaging standards. We went through several iterations of developing an idea and examining the HL7 standards to see if the proposal could be implemented using the standard specifications. While some ideas seemed clear-cut on the surface, we found that the implementation would have been complicated with a high potential for errors. Others would have been straightforward in terms of HL7 implementation but relatively difficult to code and manage using LOINC. Our final reporting method complies with HL7 and should be straightforward to implement using LOINC codes as described below.

Table 1. Observations and their LOINC codes

Observation	*LOINC code*
Hemoglobin observations newborn screening panel	64116-7
Most predominant hemoglobin	64117-5
Second most predominant hemoglobin	64118-3
Third most predominant hemoglobin	64119-1
Fourth most predominant hemoglobin	64120-9
Fifth most predominant hemoglobin	64121-7
Hemoglobins that can be presumptively identified based on available controls	64122-5

After we decided on the best reporting method, we turned to the specifics of creating observations and answer lists. LOINC observations can be considered the questions, and we had to come up with specific questions to capture all of the information necessary to convey the result accurately, including which Hbs were found and the relative amount of each. Once we created the questions, we decided on the format that the answers would take; LOINC answers can have multiple formats, including numbers, text or fixed answer lists, depending on the nature of the observation. Once we had finalized the observations and answers, we submitted them for LOINC code assignment using Regenstrief Institute's formal submission process (http://loinc.org/submissions).

Results

Our method focuses on reporting the individual Hbs as separate results rather than trying to report the overall combination of all the hemoglobins found. Based on information gathered by the workgroup, we created a LOINC panel containing 5 LOINC codes for reporting up to 5 distinct Hbs in a specimen in terms of their relative concentrations (see Table 1). Depending on the number of Hbs found in a given sample, anywhere from one to all five codes can be used in separate HL7 message segments (see Figure 1).

Figure 1. Reporting the Hb types found in a single sample. Example 1 shows reporting a result with two types of Hb, and Example 2 contains 3 types.*

Example 1: Hb F,A

OBX|1|CE|64117-5^ Most predominant hemoglobin ^LN^^^ |1| LA16208-3^**Hb F**^LN ||||||F||| 20090714145203
OBX|2|CE|64118-3^Second most predominant hemoglobin^LN^^^ |1|LA16209-1^**Hb A**^LN ||||||F||| 20090714145203

Example 2: Hb F,A,S

OBX|1|CE|64117-5^ Most predominant hemoglobin ^LN^^^ |1| LA16208-3^**Hb F**^LN ||||||F||| 20090714145203
OBX|2|CE|64118-3^Second most predominant hemoglobin^LN^^^ |1|LA16209-1^**Hb A**^LN ||||||F||| 20090714145203
OBX|3|CE|64119-1^Third most predominant hemoglobin ^LN^^^ |1| LA13007-2^**Hb S**^LN ||||||F||| 20090714145203

*Please note – for purposes of simplicity, the entire HL7 OBR/OBX structure is not shown. For more details, see http://newbornscreeningcodes.nlm.nih.gov/nb/sc/constructingNBSHL7messages

We created a fixed answer list for hemoglobin types based on workgroup consensus regarding the hemoglobins that are typically reported by NBS labs. Although more than 700 hemoglobin variants exist, most NBS labs do not routinely identify most of them, and even some of the ones that are detected may not be reported if they are known not to be clinically significant. Therefore, our current answer list has 20 answer codes (see Table 2) which were reviewed and approved by multiple NBS programs and labs. In cases where Hb separation is problematic (e.g. Hb D/G), limited Hb combinations were also coded.

Table 2. LOINC answer list for types of Hb

Hemoglobin type	*Answer code*	*Hemoglobin type*	*Answer code*
Hb F	LA16208-3	Hb D-Punjab	LA16216-6
Hb A	LA16209-1	Hb D/G	LA16217-4
Hb A - indeterminate	LA16210-9	Hb E	LA13005-6
Hb A2	LA16211-7	Hb G	LA16218-2
Hb A2 - elevated	LA16212-5	Hb G-Philadelphia	LA16219-0
Hb Bart's - low level	LA16213-3	Hb H	LA16220-8
Hb Bart's - highly elevated	LA16214-1	Hb Lepore Boston	LA16221-6
Hb C	LA13002-3	Hb O-Arab	LA16222-4
Hb Constant Spring	LA16215-8	Hb S	LA13007-2
Hb D	LA13003-1	Hb unidentified	LA16223-2

A code for reporting unidentified Hb variants was also created. The definition of unidentified variant(s) is unique to each lab and is dependent on laboratory method and/or reporting protocol. If a laboratory reports an unidentified variant, it must also report the Hb types it **is** able to identify using LOINC code 64122-5 (*Hemoglobins that can be presumptively identified based on available controls*) and the appropriate answer codes to help understand the unidentified result. For example, if one lab can identify Hb O-Arab, it will use LOINC answer code LA16222-4 (*Hb O-Arab*). However, another lab may not be able to identify that particular

Figure 2. Reporting Hb variants. Example 1 shows how a lab that can only identify Hb A, F, C and S would report an unidentified Hb. Example 2 shows how another lab would report the same exact result, only this lab can identify the variant as O-Arab.*

Example 1: Hb F,A,unidentified (lab that identifies A, F, C and S)

OBX|1|CE|64117-5^ Most predominant hemoglobin ^LN^^^ |1| LA16208-3^**Hb F**^LN ||||||F||| 20090714145203
OBX|2|CE|64118-3^Second most predominant hemoglobin^LN^^^ |1|LA16209-1^**Hb A**^LN ||||||F||| 20090714145203
OBX|3|CE|64119-1^Third most predominant hemoglobin ^LN^^^ |1| LA16223-2^**Hb unidentified**^LN ||||||F||| 20090714145203

OBX|1|CE|64122-5^Hemoglobins that can be presumptively identified based on available controls ^LN^^^ |1| LA16209-1^**Hb A**^LN ||||||F|||
20090714145203
OBX|2|CE|64122-5^Hemoglobins that can be presumptively identified based on available controls ^LN^^^ |1| LA16208-3^**Hb F**^LN ||||||F|||
20090714145203
OBX|3|CE|64122-5^Hemoglobins that can be presumptively identified based on available controls ^LN^^^ |1| LA13002-3^**Hb C**^LN ||||||F|||
20090714145203
OBX|4|CE|64122-5^Hemoglobins that can be presumptively identified based on available controls ^LN^^^ |1| LA13007-2^**Hb S**^LN ||||||F|||
20090714145203

Example 2: This lab can identify the unidentified Hb in example 1 as Hb O-Arab, and therefore does not need to include the list of Hb types it can identify

OBX|1|CE|64117-5^ Most predominant hemoglobin ^LN^^^ |1| LA16208-3^**Hb F**^LN ||||||F||| 20090714145203
OBX|2|CE|64118-3^Second most predominant hemoglobin^LN^^^ |1|LA16209-1^**Hb A**^LN ||||||F||| 20090714145203
OBX|3|CE|64119-1^Third most predominant hemoglobin ^LN^^^ |1| LA16222-4^**Hb O-Arab**^LN ||||||F||| 20090714145203

*Please note – for purposes of simplicity, the entire HL7 OBR/OBX structure is not shown. For more details, see http://newbornscreeningcodes.nlm.nih.gov/nb/sc/constructingNBSHL7messages

Hb and would report their result using LOINC answer code LA16223-2 (*Hb unidentified*) as well as code 64122-5 identifying the codes for all hemoglobins it can presumptively identify (see Figure 2).

Currently, most laboratories have their own unique interpretation or recommendation statements for abnormal results. Therefore, LOINC code 57703-1 (*Hemoglobin disorders newborn screening comment-discussion*) can be used to send a custom message. LOINC codes for reporting quantitative percentages for each Hb found are also available, but since most laboratories do not routinely report quantitative screening results, we have not included a detailed discussion about these codes here. However, all of the codes and information about how to use them are available at http://newbornscreeningcodes.nlm.nih.gov/nb/sc/constructingNBSHL7messages.

Discussion

Our method for reporting NBS hemoglobinopathy results is straightforward to implement and can accommodate most, if not all, of the variability in hemoglobinopathy result reporting across NBS labs. Programs can use as many or as few codes as they need. For example, if a sample contains two Hbs, only codes 64117-5 (*Most predominant hemoglobin*) and 64118-3 (*Second most predominant hemoglobin*) are necessary. However, if a sample contains 4 Hbs, the labs will also use codes 64119-1 (*Third most predominant hemoglobin*) and 64120-9 (*Fourth most predominant hemoglobin*). Also, laboratories only have to report the Hb variants they can presumptively identify when an unidentified Hb is found. This can be an automated process in which each lab can create a set of HL7 segments using code 64122-5 (*Hemoglobins that can be presumptively identified based on available controls*) for all of the Hb variants it can identify, and the inclusion of this set of segments in the result message will only be triggered when *Hb-unidentified* is reported. Laboratories would only have to update this set of segments if they add a new Hb type to the list of Hb they can presumptively identify. LOINC code 57703-1 (*Hemoglobin disorders newborn screening comment-discussion*) provides the flexibility for programs to send their unique interpretation and recommendation messages, which would be sent in addition to the primary results.

Another major benefit to this reporting system is its ease of maintenance as more Hb variants are discovered. As opposed to previous attempts to code all possible Hb patterns, this method simply requires a single answer code to be added to the Hb answer list if a new Hb is available for reporting.

One issue encountered was that actual results generated by an automated methodology may be reported directly from the machine. In some cases, such automated results do not follow accepted Hb nomenclature rules. For example, one machine reports *Hb a* (lowercase "a") when the identification of Hb A is uncertain. However, according to the original nomenclature guidelines,[5] lower case letters should not be used to identify hemoglobins. Therefore, we created answer code LA16210-9 for *Hb A – indeterminate* to cover this result, and the lab can also report the exact machine result using code 57703-1 (*Hemoglobin disorders newborn screening comment-discussion*). The same machine uses *Hb B* and *Hb b* to represent various levels of Hb Bart's. However, because Hb b was the original name for sickle Hb, once the name was changed to Hb S, the guidelines specified that the letter B was not supposed to be used again lest it be confused with Hb S.[5] We created LOINC answer codes LA16213-3 and LA16214-1 for *Hb Bart's – low level* and *Hb Bart's – highly elevated*, respectively, so that laboratories can use our answer codes and also report the exact machine result, again using code 57703-1.

We presented our work to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children's Laboratory Standards and Procedures subcommittee, and they accepted this method as the best approach for reporting hemoglobinopathy screening results using LOINC and HL7. Subsequently, we included this method in the HRSA/NLM guidance for reporting NBS results,7 which can be found at http://newbornscreeningcodes.nlm.nih.gov/nb/sc/constructingNBSHL7messages. Many NBS programs in the U.S. are in the process of implementing this guidance, and we have received positive feedback from them regarding the simplicity and flexibility of our method for reporting hemoglobinopathy screening results.

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