Roadmap to the Draft Reference Matrix for Newborn Screening
6/10/2008

Overview

The reference matrix for newborn screening is a set of tables that will be used to develop Interoperability Specifications for the Newborn Screening Use Case and will be maintained in the future to provide clear specifications for reporting the results of newborn screening tests and monitoring newborn screening programs. Availability of the matrix will help guide specifications for a uniform electronic newborn screening report that can be used for patient focused care as well as for population health. The data on the newborn screening report will also become the foundation for a consultation and referral document that will make the initial screening results available to all future providers and facilitate including confirmatory testing results, final diagnosis, and treatment interventions along with a listing of all relevant providers, encounters, and procedures that have occurred. The reference matrix will be the source for all terminology and coding for both the initial screening report and the consultation and referral summary document, but our initial focus has been on the initial screening report based on newborn dried blood spot screening tests and newborn hearing screening. Gaps in coding and standards that were identified and resolved during development of the reference matrix will expedite implementation of the use case by facilitating early involvement of standards development organizations, such as LOINC, to address the requirements of the use case early in development. It is also important to remember that details of quantitative reporting and appropriate units of measure or identification of specific genetic markers do not need to be displayed or reported to all clinicians when this information is not useful, but details will be included in the electronic reports to support other uses. Electronic newborn screening reports can generate paper documents or web pages that are customized to the user viewing the report and the normal or abnormal nature of the results.

The matrix uses the term **Analyte** to refer to test result data that is reported on a newborn screening report. The analyte name is essentially the name of the value that will be reported on the test report. Analytes in electronic laboratory reports are identified by LOINC codes that are assigned by the Logical Observation Identifiers Names and Codes (LOINC) Committee. LOINC codes are very precise and specific and may be used to identify the methods, units, specimen type or system, type of observation, and other details that clarify which test was used and the level of quantitative reporting. An important function of the reference matrix will be to specify the appropriate level of detail to report in an electronic newborn screening report and to clarify which test was done in a particular state at a particular point in time.

Some analytes are referred to as 1st Tier or 2nd Tier tests. This does not imply collection of a second specimen but instead means that the 2nd Tier test is done on the same specimen only if the 1st Tier test is abnormal. This type of test is often called a reflex test by laboratories because it is ordered automatically based on the result of the first test. This is analogous to doing sensitivities automatically on most organisms recovered on a culture. Some states do use a second specimen newborn screening process and the reports

generated using terminology in the reference matrix will include proper identification of results from the first and second specimens.

The matrix uses the term **Condition** to refer to the diagnosis or condition that the analyte is intended to screen for. It is important to identify both the analyte name and the condition name as either one might be used to refer to a test result and the conditions that should be reported. Many conditions represent rare disorders that are not clearly represented in common diagnostic coding systems such as ICD9. We have included many different available coding systems that may be required to accurately describe a condition and in some cases the specific genetic variant. Current electronic laboratory reporting and medical summary standards allow the use of several different coding systems to describe a condition and the reference matrix will guide optimal use of existing standards. Some conditions have been identified as primary, secondary, or other targets by the American College of Medical Genetics (ACMG) and this information has been used to group conditions. Another use of the condition lists in the reference matrix will be to link to educational materials and decision support materials for rare disorders such as the ACMG ACT Sheets.

An important feature of the reference matrix is an attempt to merge together the wide range of tests and conditions covered in newborn screening programs. We have included Early Hearing Detection and Intervention (EHDI) along with other forms of newborn screening for metabolic, endocrine, hemoglobin, congenital infections, and other conditions. In the future, we anticipate more examples of bedside testing to accompany the newborn dried blood spot screening tests and the reference matrix will be a guide for including all newborn screening tests in a single report where data and required referrals will be easier to track. Although the level of alternate terminology and coding varies among categories of newborn screening, the reference matrix demonstrates strong similarities in the data requirements of all types of newborn screening and the ability to represent this data in a single matrix. The matrix remains a work in progress that will continue to expand and change as the methods of newborn screening evolve.

The utility of a newborn screening report is greatly enhanced by including the birth history and newborn conditions and treatments that may affect the accuracy and interpretation of the tests. The addition of family history to a newborn screening report also adds value, particularly for detection of hearing. At the present time, newborn screening programs, unlike many antenatal screening programs, apply a uniform battery of tests to all newborns. In the future, the tests performed on a given infant may vary with family history or other parameters and the reference matrix will be expanded to include specifications on data that should be included in personalized newborn screening reports.

MSMS Analytes tab

This table describes newborn dried blood spot analytes measured by tandem mass spectrometry (MS/MS) that is the main method used for identifying metabolic disorders. The table is sorted by molecular weight in the order in which the analytes are reported by the equipment in the lab. Many of the analytes are ratios of other values that have been included because of their diagnostic value and because they are typically included in the

reports. The analytes are also classified into four categories (AA=Amino Acids, FAO=Fatty Acid Oxidation, OA=Organic Acidemia, and AC=Acyl Carnitines) based on the type of condition they are associated with. Many of the rows represent ratios of other values and some analytes are so close together on the MS/MS readings that they can only be expressed as a sum of multiple analytes. The most important feature of this table is the specification of LOINC codes for reporting results along with the units and other properties and scale implied by the LOINC code. This table does show all values as point in time measures (Pt) and quantitative (Qn), but some are concentrations (SCnc) and some are ratios (ScRto). The status of normal or abnormal is added to the report by the laboratory based on their cut off values and placed in appropriate fields in the electronic report. Note that a number of analytes that can be reported have no known clinical significance and can be included in reports for future value but not displayed to clinicians at the present time.

MSMS Conditions tab
This table identifies the range of conditions that can be detected by tandem mass spectrometry grouped by the ACMG primary, secondary, and other target status as well as categories of the condition. The condition has its own name that may be identical with the name of the involved enzyme and also identical with the analyte detected by the MS/MS test. The codes in this table represent diagnostic codes instead of the LOINC codes used in the analyte table to represent test result values.

MSMS Analyte to Condition tab
This table is a supplement to the reference matrix that presents a proposed mapping of the analytes reported from the screening test to the conditions they suggest. Note that there is lack of agreement on how to interpret all MS/MS results and this table should be considered a guide to possible future decision support tools but not a definitive diagnostic mapping. Each row in the table represents one of the analytes from the MS/MS analytes table and they appear in the same order but are limited to 1st Tier analytes. The columns represent the conditions in the MS/MS conditions table grouped by ACMG primary, secondary, and other targets as well as by the category such as AA, FAO, and OA. As the “count” column reveals, a single analyte result may be associated as a primary or secondary marker for a number of different conditions. Also many conditions produce abnormalities in many different analytes.

Non-MSMS Analytes tab
This table presents the variety of result values from a range of non-tandem mass spectrometry newborn screening tests and is much more variable than the MS/MS analytes table but has a comparable structure. Many report qualitative results and LOINC codes have not yet been established for all of them, but work is in progress. Several of these analytes may be measured by different methods but will be reported the same way. The reference matrix will help to identify the key distinctions that should be made between testing and reporting methods for all newborn screening tests in common use.

Non-MSMS Conditions tab

This table lists a wide range of conditions that can be detected by methods other than tandem mass spectrometry. Note that several of them involve specific enzymes as do many of the MS/MS conditions. Also as with the MS/MS conditions, a variety of different disease coding systems may be needed to distinguish conditions that are lumped under a single heading in some coding systems.

EHDI Tests tab
This is a temporary table in the matrix that includes a wide range of hearing tests used for initial screening, diagnostic testing, and also habilitation procedures such as fitting appropriate hearing aids or cochlear implants. Until the LOINC coding is complete, they are being identified by CPT billing codes and the tests, along with all of their results reporting parameters that are the analog of the analytes from tandem mass spectrometry, will also require LOINC codes and be added to the non-MS/MS analyte table.

EHDI Units of Measure tab
This is a temporary addition to the matrix that covers the typical units that are used to report hearing testing results. It will be integrated into the EHDI tests and then merged with the Non-MS/MS analytes as soon as LOINC codes are identified or created for reporting hearing testing.

EHDI Genetic Causes tab
This table lists genetic causes for hearing impairments and includes a level of detail not required on the non-MS/MS conditions tab because all hearing impairments are detected through a common set of tests. Note that some named syndromes are associated with many different genetic markers and that some conditions are non-specific and used to group many different associate markers. Some of the markers involve chromosomal DNA and some Mitochondrial RNA and are thus identified by different coding systems