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ABSTRACT

Capture, coding and communication of newborn screening (NBS) information represent a challenge for public health laboratories, health departments, hospitals, and ambulatory care practices. An increasing number of conditions targeted for screening and the complexity of interpretation contribute to a growing need for integrated information-management strategies. This makes NBS an important test of tools and architecture for electronic health information exchange (HIE) in this convergence of individual patient care and population health activities. For this reason, the American Health Information Community undertook three tasks described in this paper. First, a newborn screening use case was established to facilitate standards harmonization for common terminology and interoperability specifications guiding HIE. Second, newborn screening coding and terminology were developed for integration into electronic HIE activities. Finally, clarification of privacy, security, and clinical laboratory regulatory requirements governing information exchange was provided, serving as a framework to establish pathways for improving screening program timeliness, effectiveness, and efficiency of quality patient care services.

Virtually every infant born in the USA undergoes a series of screening tests shortly after birth to identify potentially debilitating or fatal inherited conditions. Newborn screening (NBS) programs represent more than a set of laboratory tests. It is a system of education, screening, follow-up, diagnosis, management, and ongoing evaluation of the effectiveness of all components. This requires longitudinal health management of children over time and communication among public health officials, medical specialists, and the primary care physician. This need for integration among professionals and over time makes NBS a logical application of standards harmonization for health information exchange (HIE).

NBS began in the 1960s with the introduction of screening for classic phenylketonuria (PKU), an inborn error of metabolism that, untreated, leads to severe mental retardation. If detected in the newborn period, PKU can be treated effectively with dietary management. Since the introduction of PKU testing, dedicated tests for additional conditions have been added to NBS programs. These include metabolic tests, genetic analyses, and functional tests such as screening for hearing deficits. Most recently, the advent of tandem mass spectrometry (MS/MS) technology has made it possible to screen for more than 50 metabolic diseases. NBS has been shown to be cost-effective, but only if a timely, efficient system exists for assuring diagnostic confirmation, treatment, and follow-up.[1] Most laboratories operate by fee collections to support the testing.[2] The national costs for newborn screening services in 2001 were estimated to be more than $120 million, with approximately two-thirds of these costs supported by fees.[3]

The NBS process begins in the birth hospital or facility. A few drops of blood are obtained by pricking the newborn infant's heel. The blood is dried onto standardized filter paper attached to a sheet where demographic and specimen information is provided. The infant is also tested for hearing deficiencies using electrophysiological measurement of acoustic impedance. In many states, the results of the hearing screen and other information are recorded on the same card, which is sent to the NBS laboratory.

At the laboratory, aliquots are punched out of the dried blood spots. Metabolic, endocrine, and/or genetic testing is done on these specimens, depending on the testing panel adopted by a given state. Specific criteria (analyte levels and calculated analyte ratios) for judging the results of a test as positive or negative also vary from state to state. An abnormal test result is sent to the physician of record, who is frequently associated with the birth hospital but is not the primary care physician who will assume management responsibilities for the infant.

The multidirectional communication requirements for successful newborn screening and follow-up have created challenges for state systems, especially as the number and complexity of screening tests have grown. Compelling abnormal results are aggressively followed up by public health personnel. However, the resolution of indeterminate results or the completion of confirmatory testing may lag for weeks before the test is repeated, simply because communication with the family or the primary care physician may proceed slowly. An adequately trained physician seeing a newborn for the first time in the ambulatory setting typically follows up on the newborn screen results status by calling the NBS laboratory. Alternatively, in some states, physicians have the option to check NBS results by accessing a secured website.

Newborn hearing screening is probably the most notable example of failure to complete the

newborn screening process. Although nearly every infant is screened for hearing deficits, only about 50% of infants referred after initial screening have the secondary testing needed to confirm hearing loss and initiate the necessary early intervention.[4 5] This may be in part because newborn hearing screening methodology has a 2–5% false-positive rate in the general population resulting in a low positive predictive value. Given that one in 500 newborns would benefit from amplification devices, losing the opportunity to start early intervention in 50% of infants with hearing loss is a large deficiency in the system.

Communication needs for newborn screening suggest a high potential value for health information technologies, and several characteristics of the NBS process make it an ideal pilot application for HIE and thus for a national use case analysis. First, virtually every child born in the USA can potentially benefit from an optimized system. For some diseases the process is time-critical. Adverse consequences are best averted by early identification and intervention.

Most conditions on each state's recommended NBS test panel occur rarely when considered individually. This means that a typical physician may not have the opportunity to encounter even a single case of some conditions in their entire career. As a result, immediate availability of information on diagnosis and acute management is critical. It also means that timely referral to appropriate metabolic, endocrine, genetic, or other specialty care must be coordinated. These specialty resources are sparse in many parts of the country. Specialists seeing these patients will, in many cases, benefit from access to complete screening test results. These needs and others can be met through HIE, which is defined as the electronic movement of health-related information among organizations according to nationally recognized standards.[6]

One of the greatest challenges to NBS programs is locating the child whose screen is abnormal, borderline, or inadequate. Frequently, the child's mother may not have identified a primary care physician yet, so the task to initiate follow-up is left to a physician affiliated with the birth hospital but he/she may have no direct knowledge of the newborn and his/her family. In a worst-case scenario, an infant who has entered a metabolic crisis because of an inborn error of metabolism is likely to show up in an emergency room before the primary care physician knows the infant exists. An HIE has the potential to deliver the NBS data to the physician who is actually caring for the infant regardless of the setting.

Long-term follow-up is another aspect of care of affected infants in which HIT can support NBS program objectives. Most conditions identified through NBS are lifelong disorders that require therapies or other health considerations indefinitely. In a mobile society, affected individuals must be tracked far away from their birth place. Because NBS programs are state-based, ongoing care requires coordination and transfer of information across state lines. Access to medical records and treatment requirements (eg, special diets) must follow the patient. This was recently illustrated in the aftermath of Hurricane Katrina.[7] Moreover, as affected children transition to adulthood, metabolic and other requirements unfamiliar to most adult medicine specialists must be transitioned as well.

NBS laboratory quality improvement and quality assurance efforts can also be profoundly improved through aggregation of data across NBS programs. Mechanisms do not exist, except in pilot projects, to aggregate individual level data across NBS programs. Standard representation of screening test result data would make this possible.

Research on many of the conditions detected through newborn screening is difficult because they are rare, some occurring in less than once in 100 000 births. Yet, more research is needed to understand the natural history of many of these rare conditions and especially to test the effectiveness and safety of new treatments. Even evaluating the value of specific screening tests will require aggregation of data across programs. This will only be achieved if standard data representation and communication processes are defined. Similarly, the rapid pace of science and technology and the momentum for adding new conditions to the recommended uniform panel creates a need for HIE to collect evidence to support decision-making.

Management of NBS programs is different from most if not all other public health programs. Each state establishes its own panel of tests and rules for timing or repeating specimens. Under the directive of the Newborn Screening Saves Lives Act of 2008,[8] most states have now implemented the 29 test core panel recommended by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) based on a report by the American College of Medical Genetics (ACMG).[9] Uniformity of adoption of the recommended panel has also greatly increased the volume of newborn screening data and created a role for HIE to support the enhanced management needs of NBS programs.

Timely and unencumbered access to test results information by any of the many potential healthcare providers of a patient is essential to derive full benefit from all information generated by newborn screening. The HIE exchange of screening test results is mostly conceptual at this stage, although the stage is set for breakthroughs in several settings. Some states have conducted production level electronic data exchange from birthing facilities to laboratories and in turn transmitted test results to those facilities (J Bail, D Shirazi, personal communication, 2008). At present, we know of no program that enables incorporation of laboratory test results into a patient's electronic health record (EHR). A number of states support web-based registries, some associated with immunizations, birth, and death registries that enable secured access to results. While these resources offer providers a means to verify test performance and results, they do not allow integration of results into EHRs or allow longitudinal tracking of results and patient outcomes. Despite the current lack of connectivity, however, substantial preparatory work to support HIE has already occurred through the establishment of common terminology standards and testing methods, thereby setting the stage for greater accessibility and portability.

DESIGN OBJECTIVES AND SYSTEM DESCRIPTION

In 2006, the American Health Information Community (AHIC) Personalized Health Care Work Group was formed and given a broad charge to: "Make recommendations to the American Health Information Community for a process to foster a broad, community-based approach to establish a common pathway based on common data standards to facilitate the incorporation of interoperable, clinically useful genetic/genomic information and analytical tools into EHRs to support clinical decision-making for the clinician and consumer."[10]

In 2007, as directed by the Secretary of Health and Human Services, the work group prioritized information exchange for newborn screening test results for standards harmonization and development of interoperability specifications.[11] AHIC found that there were compelling public health and medical management needs for integrated test ordering, quantitative laboratory results reporting, and clinical decision support for managing confirmatory testing and medical intervention strategies.[12] A recommendation was made, calling for development of a

Newborn Screening Use Case for referral to the Health Information Standards Panel (HITSP) to harmonize standards and establish interoperability specifications.[13] The detailed use case was finalized and referred to HITSP in December 2008.

Another recommendation called for development of a reference coding and terminology resource for all tests routinely used in public health screening, analytes, conditions screened for, and associated genetic variants that are used in newborn screening programs. This recommendation led to the newborn screening coding and terminology guide that supports the use case and is intended to enable linkage among the various relevant terminologies, processes and definitions used in different NBS programs ultimately establishing semantic interoperability. AHIC likewise recommended electronic reporting of quantitative results of newborn screening, that is, instead of reporting only the "conclusion" that "disease X might be present"—as is the common practice at present, also report the amount of each of the analytes measured as part of newborn screening and upon which those "conclusions" are based. Furthermore, a large scale, collaborative effort is under way to reach a consensus on the panel of analytes and analyte ratios that constitute the most complete and informative phenotype of a given condition (see http://www.region4genetics.org/msms_data_project/data_project_home.aspx). Notably, this project has already incorporated LOINC and SNOMED codes in the definition of analytes and conditions. Such quantitative reporting will allow cross-referencing of results across various testing methods to support patient care and evaluation of screening programs.

A third recommendation called for the summation of federal privacy, regulatory, and laboratory test regulations that are applicable for newborn screening HIE to assist expansion of interoperability among the many stakeholders in newborn screening.

Taken together, the resources that have been developed in response to these recommendations provide a beginning framework for pilot implementation of newborn laboratory test result reporting through HIEs to serve expanded applications of the information in patient care, research, and program evaluation.

Advancing standards and interoperability specifications to support management of newborn screening programs

The use case developed in response to the AHIC work group's recommendation defines the goals and processes involved in the information exchange requirements for NBS programs. Greater use of EHRs with standards and interoperability specifications for newborn screening laboratory results and patient management can be expected to make important contributions toward quality improvements and increased efficiency in screening programs. The multifaceted impact of HIE activities is demonstrated by the following typical scenario from the use case[13]:

> A newborn infant is born at a hospital, and simultaneous with the patient's hospital record registration in an electronic record system, an order set is generated that notifies nursing and laboratory personnel of required newborn screening tests to be performed. Upon collection of a newborn dried blood spot specimen, the patient's record and lab request is annotated with patient-specific information (diet, medications, antenatal history, etc) then, transmitted electronically to the state public health laboratory. In the laboratory, the patient's request is registered in a database and the screening tests are performed. Once verified, the screening test results are transmitted through a health information exchange enabling results to be archived in state program laboratory testing registries, transmitted to ordering provider and follow-up providers and messaged to state public health programs. The screening test results yield an abnormal result consistent with a biochemical diagnosis of medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD) which requires follow-up testing. An alert is transmitted from the laboratory that notifies the individuals and organizations with actionable steps to confirmatory testing. The results when presented to the primary care provider are reviewed with the parents and recorded electronically into the patient records. A referral is generated for specialty referral and diagnostic testing. The information about the patient's results are transmitted to the referral center electronically and tracked by the public health laboratory for verification of confirmatory testing results. The patient follows up with the referral specialist, and a diagnostic test specific for MCAD is performed. The tests confirm an inherited trait and the results are then transmitted to the primary care practitioner, referral center, and state department of health where the screening test results are reconciled with the confirmatory tests. Patient management information is provided electronically to support nutritional intervention, registration for medical assistance for acquiring modified infant formulas, and medical and developmental follow-up. Over the course of the next several years, longitudinal data to support follow-up and patient outcomes of dietary, medical, and developmental management are transmitted to the health department and referral center. Information exchange will also support provision of information for parents via portals or other forms of electronic information transfer.

The scope of the newborn screening use case also addresses the information requirements to support ordering, test results reporting, and follow-up of early hearing detection intervention programs. Establishment of interoperability specifications and harmonization of standards for laboratory information about newborn screening can be considered an area of mandatory interoperability because information must flow between the hospital or birthing center, public health agencies, primary care physicians, and specialists (including audiologists) who care for the over four million infants who are screened each year. The use case includes both individual patient-focused care and population health improvement consistent with the Office of the National Coordinator (ONC) Strategic Plan.[14] These NBS standards development activities build on and relate to prior AHIC use case standards harmonization and interoperability specifications for laboratory test reporting, electronic records, and quality measures.

Coding and terminology standards for newborn screening tests

A coding and terminology framework is essential to standardizing laboratory reporting and enabling interoperability of information exchange across EHR platforms. The coding and terminology guide will also facilitate clinical decision support and provide linkage to other information for all core conditions. The approach to naming conditions that are targets of newborn screening has evolved with the evolution of medical knowledge. Some conditions are named for clinical syndromes, some for enzyme defects, and some for the abnormal analyte or substance that is measured.[15]

One of the AHIC recommendations for the NBS use case called for electronic reporting of *quantitative* results, even if they are not used clinically, so that they will be available in aggregate to support continuous quality improvement efforts. The use case calls for dual reporting of qualitative results by condition or high level categories of conditions to simplify clinical review and separate quantitative or test specific results that are displayed to the clinician only when needed but are routinely provided to public health, subspecialists, and researchers subject to privacy protection and deidentification.

Method for building the terminology guide

The Coding and Terminology Guide for Newborn Screening was developed by the AHIC workgroup through examination and harmonization of newborn screening condition terms and acronyms to existing terminologies and standards. The condition terms and acronyms developed by the ACMG were used as the master indexing terms for the Newborn Screening Terminology and Coding Guide. They were aligned to existing standard terminologies in an effort to address various levels of granularity, assign unique identifiers and thereby foster interoperability. A mapping was developed to connect codes for conditions with qualitative reporting of positive or negative screening as well as the specific quantitative tests performed. In the case of MS/MS a key requirement is to recognize that a single condition may produce multiple abnormalities and a single analyte may be associated, when either higher or lower than normal, with multiple conditions. For example, almost half (47%) of the markers detectable by MS/MS require a differential diagnosis between three or more conditions, and the biochemical phenotype of a third of these conditions may include five or more informative markers.[16 17] Harmonization efforts have been aimed at the following terminology and coding standards: International Classification of Diseases (ICD-10), Systematized Nomenclature of Medicine (SNOMED), Logical Observation Identifiers Names and Codes (LOINC), Online Mendelian Inheritance in Man (OMIM), and HL7 messaging standards.[18]

International Classification of Diseases-10 (ICD-10), an international standard diagnostic classification for general epidemiologic considerations for health and disease states is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates. This enables the storage and retrieval of diagnostic information for clinical, epidemiological, and quality purposes.[19]

The Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) is considered to be the most comprehensive, multilingual clinical healthcare terminology in the world. SNOMED-CT aims to facilitate communication and interoperability in electronic health data exchange.[20]

Logical Observation Identifiers Names and Codes (LOINC) facilitates the exchange and pooling of clinical results for clinical care, outcomes management, and research by providing a set of universal codes and names to identify laboratory tests and other clinical observations.[21]

Online Mendelian Inheritance in Man (OMIM) is a comprehensive, authoritative, and frequently updated compendium of human genes and genetic phenotypes. The overviews of genetic disorders in OMIM contain information on all known Mendelian disorders and over 12 000 genes with references to classical descriptions of clinical presentations.[22]

Maintaining the coding and terminology guide

The ACMG terms that have guided the development and definition of the core test panel do not represent a unique vocabulary or coding system. The level of granularity of defining conditions that was used by the ACMG can be matched through the addition of new codes to SNOMED-CT and other vocabularies with the ACMG acronyms serving as useful short names for rapid recognition of testing programs and efficient and compact report formats. Current National Library of Medicine (NLM) Unified Medical Language System (UMLS) structure and technologies can also accommodate the various synonyms used to refer to conditions, and relationships can map conditions to laboratory test results and their associated LOINC codes. The coding and terminology will be maintained by the NLM in collaboration with the Health Resources and Services Administration (HRSA) and the Centers for Disease Control and Prevention (CDC) as part of the UMLS with collaborative quarterly review by ACHDNC that approved the ACMG newborn screening panel.[23] Having a national coding and terminology guide will facilitate uniform reporting and data sharing between states and interpreting reports when children move or seek care in different parts of the country. Existing clinical vocabularies have not had the appropriate degree of granularity for rare conditions that are being evaluated as targets of screening programs. The acronyms of convenience that have assisted past deliberations and evidence gathering are now being replaced by efforts to create new codes and new hierarchical classifications as new tests or conditions enter the process of evaluation as candidates for screening.

NLM will provide all of this content to the public as a set of human and machine readable tables that provide LOINC codes for reporting both qualitative interpretations as well as quantitative values of the analytes measured as part of NBS. These tables include units of measure for tests with numeric values and answer lists for tests with categorical results. The tables also link test measurements to the disorders they detect and contain existing ACMG codes to identify the purpose of the testing, SNOMED CT codes for categorical values, SNOMED CT and OMIM codes for genetic disorders and ICD-10 codes to provide links from the more specific code systems to traditional diagnostic coding systems. These tables are deployed at http://newbornscreeningcodes.nlm.nih.gov/ for human reading and computer downloading. We encourage NBS laboratories to use the universal codes provided in these tables to identify the test measurements and results they report within HL7 messages so that all recipient systems can understand them. Mayo Medical Laboratories was able to quickly implement such a system for reporting their NBS testing, proving its feasibility.

Privacy, security, and laboratory oversight considerations for newborn screening HIE

Although newborn screening is subject to all of the regulatory considerations for electronic laboratory results reporting, its provision is complicated by frequent changes in providers, jurisdictional boundaries, and the genetic elements of the information that is gathered. Privacy is a particular concern for genetic data. The use of deidentified newborn screening data greatly benefits research and population health improvement activities. However, critics have questioned the ability to truly deidentify genetic information and fear potential discrimination based on knowledge of genetic information. The Genetic Information Nondiscrimination Act of 2008 (GINA)[24] is a step forward in protecting individuals from genetic-based discrimination in health coverage and employment decisions. GINA will help reduce fear-based barriers to electronic sharing of newborn screening results.

Informing patients of the use and disclosure of their newborn screening data is important since consent for testing is required in only a few states. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Rules and the Clinical Laboratory Improvement Act of 1988 (CLIA) are the federal regulations that impact newborn screening electronic reporting. Two challenge areas are the transmission of results across state lines and reporting results to a provider who was not the ordering provider or identified at the time the specimens were obtained. Both situations are common because newborns may receive their care in a state different from the location of the hospital or birthing center where they were born,

and changes in the primary care provider are frequent in the first 2 weeks of life. A resource document of federal privacy, security, and laboratory oversight regulations as they apply to newborn screening information exchange has been developed to facilitate understanding and application in HIE scenarios.[25] State laws and regulations must also be considered. The application of the regulations may also depend on whether the results are being disclosed by the hospital where a child was born, the laboratory that performed the test, or the state newborn screening program or other public health entity.

DISCUSSION

The problems that are seen with failure to manage and follow-up on routine laboratory results are magnified in newborn screening situations when negative outcomes could be triggered by incomplete reporting, failure to recognize a critical result, and delays in completing the confirmatory or referral process. These situations could result in catastrophic clinical outcomes or significant missed opportunities for early diagnosis and effective care in the longer term. There are opportunities for quality improvement at each phase of newborn screening. During the initial screening process electronic data exchange helps to "close the orders loop" and make sure that all infants are tested and that a responsible clinician has looked at the results of the tests. For confirmatory testing, educational materials on the diagnosis and management of rare disorders can be provided along with the results of the test.[26] The results of all hearing and metabolic testing can be brought together to simplify decision-making. Decision-support tools can be used to evaluate the need for repeat testing in some infants who were tested too early (<24 h of age) or had illnesses or treatments that could interfere with initial testing. During patient referral processes and initial management after a diagnosis is made, specialists can receive the results of all prior testing, and children can be registered with state programs for children with rare diseases or needing diet or educational support. An emergency care plan in a standard electronic format can be created for use when emergency care is needed or new providers are seen. Finally, knowing the outcomes of newborn screening can provide essential evidence for public health decision-making about which screening tests to offer in the future.

Implementation of interoperable electronic newborn screening laboratory reports involves more than just messaging standards and coding vocabularies. It requires development of multiple interfaces throughout the workflow processes in the health department, hospitals, clinical practices, and a network to transmit data among all parties who must communicate. Adoption of standards is also accelerated by use of conformance testing tools to guide and verify correct use of standards and pilot testing to confirm standards readiness to meet user needs.

The need for disaster preparedness for newborn screening programs has been well documented by the disruptions in the screening process and in patient care after major natural disasters.[27] Uniform data formats and coding enable health departments to make arrangements for backup and continuity of operations during a disaster with easy access to existing data on screening results that have been completed and identification of children not yet screened. Patients diagnosed as having rare disorders could benefit if a complete medical summary and an up-to-date list of medications and dietary requirements were readily available during an emergency. Patients and health departments should have a plan for completing the newborn screening process and maintaining specialized care for patients who require it during an emergency.

CONCLUSION

Clearly, HIE has the potential to improve the quality of newborn screening programs. With the advent of PKU testing in the 1960s, newborn screening became a highly visible success for public health; with time, however, the number and complexity of tests and the demands on results-reporting have grown to a point where communications-related failures are not uncommon events with potential dire effects for patients. A successful NBS program depends on reliable and secure multidirectional flow of patient information among data users, as well as long-term availability of such information as life changes occur for the patient.

Over the past decade, significant progress has been made toward harmonizing the heterogeneous state newborn screening programs by application of new technologies and testing procedures. In particular, beginning in 2007, work carried out through the AHIC has laid a foundation of standards, coding, and terminology that enable implementation of HIE in this public health and patient care domain. Such implementation could be undertaken quickly and effectively, especially by focusing first on the relatively small number of state public health laboratories and contractor laboratories that have centralized results reporting. With such implementation, substantial improvements in timeliness and efficiency of NBS can be delivered as a result of HIE for all infants with improvements in effectiveness enabled through long-term follow-up of outcomes. It is even possible to look toward a future in which implementation of electronic NBS results could be combined with other key pediatric information like immunization records, and thus create an electronic record for every newborn infant in the USA.

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