Newborn Screening in Arkansas SFY09

A Report of Activities Leading to Expansion of Screening, with Results from the First Year
July 1, 2008-June 30, 2009

Child and Adolescent Health Section
Family Health Branch
Arkansas Department of Health

Introduction

Screening of newborns for inborn conditions to avert serious complications has been considered an essential public health activity in America for nearly half a century. In Arkansas, State Fiscal Year 2009 marked a major step forward with regard to such screening. In that year, the state implemented a massive expansion of the screening program, mirroring trends in other states. This report describes the activities leading up to program expansion, the partners involved, the conditions added, laboratory and follow-up methods, and the results from screening during the first year of expanded activity. A brief discussion of the results, lessons learned, and possible future directions is also presented.

Background

Early History of Newborn Screening in Arkansas

In the absence of federal mandates to screen for any particular disorders, Arkansas historically added conditions for newborn screening one by one, always as a result of legislative action. A similar process was also employed in virtually every other state during the early decades of screening. The first disorder for which newborn screening was mandated in Arkansas was Phenylketonuria (PKU), as per Act 192 of 1967. The next disorder, Congenital Hypothyroidism (CH), was added as a result of Act 481 of 1981. Screening for Sickle Hemoglobin Diseases was authorized in 1987 (Act 573), but screening was not implemented until 1988. Later on, Act 113 of the 1995 General Assembly mandated screening for Galactosemia, which was implemented January 1, 1996. Finally, the law mandating hearing screening for most Arkansas newborns was passed in 1999. To assure screening for all of these conditions, the Arkansas Department of Health (ADH) was designated the lead agency.

Setting the Stage for Expanded Screening

Beginning in the early 1990's, new technologies with applications for newborn metabolic screening emerged on the national scene, most notably tandem mass spectrometry. A few larger states piloted this methodology and reported favorable results by the end of the century. In addition, other disorders (e.g. Cystic Fibrosis, Congenital Adrenal Hyperplasia) detectable through other test methods were also piloted in a few states, again with favorable evaluations. Still, many states were slow to adopt screening for these newer conditions. In an effort to help standardize newborn screening across the states, and to give states guidance on which conditions were most appropriate for mass screening, in 2001 the federal Maternal and Child Health Bureau commissioned the American College of Medical Genetics (ACMG) to develop comprehensive recommendations. The ACMG

undertook an exhaustive analysis of candidate conditions for screening, and following a rigorous review produced, in 2005, a list of 28 "core" metabolic conditions for which screening in all states was recommended. An additional 25 "secondary" conditions which did not meet sufficient criteria for universal screening were also listed. States were advised to consider screening for the secondary conditions at a later date when additional information on the benefits of screening became clear, or possibly sooner if resources allowed.

The Modern Era

In the 2003 Arkansas General Assembly, the newborn screening law was amended to allow the Arkansas Board of Health to designate additional disorders for screening, obviating the need for specific legislative action each time. Nonetheless, such action did occur in 2005, when Act 1931 authorized newborn screening for Cystic Fibrosis (CF) "if funding is available." At the time, sufficient funds did not exist to allow initiation of CF screening. However, upon release of the ACMG report the (then) Division of Health began serious discussions about the need for expanded newborn screening to include all the core disorders, including CF. In 2006, the Chief of the Family Health Branch was charged with drafting a White Paper that laid out the case for expanded screening. This paper was presented to the Board of Health in the fall of 2006. At that meeting, the Board approved the Division of Health's request to proceed with activities needed to screen for all 28 core metabolic conditions recommended by ACMG. The Board of Health also approved an increase in the newborn screening fee (to $89.25/specimen) to fund the expansion. Next, the 2007 General Assembly supported expansion through formal authorization of new positions within the Department of Health that were needed for implementation. Later in 2007, the Board of Health officially approved revisions to the Rules and Regulations pertaining to newborn screening that encompassed screening for the additional conditions. Beginning July 1, 2008, newborn blood specimens received in the Public Health Laboratory were screened for all 28 conditions.

Implementation Activities

In addition to the formal actions outlined above, much work was required at the programmatic level to make expanded screening a reality. During the summer and fall of 2006, ADH staff developed detailed lists of personnel, equipment, supplies, and services needed, ultimately arriving at a firm cost projection. This figure was translated into a cost per specimen that was presented to the Board of Health as a fee change request that fall. Because the proposed increase in the fee was sizeable, contact was made with the state Medicaid agency, as well as with private third-party payers, to get their "sign-off" on the

plan. In addition, the Arkansas Hospital Association was approached regarding the fee increase, and this group also voiced their generous support.

Because the 2007 legislation allowed for hiring of new positions as early as July of that year, recruitment of additional follow-up personnel commenced at that time. As a result, two new nurses joined the staff in December 2007, and an administrative support person was added in February 2008. The last follow-up nurse coordinator was hired in July 2008, followed by a Nurse Program Manager in October 2008. In the ADH Public Health Laboratory, a Lab Tech II was hired in December 2007. That same month, a laboratorian who had been hired earlier was promoted into the role of Microbiologist II and asked to become the primary analyst for tandem mass spectrometry screening.

Orientation and training of newly hired follow-up personnel occurred during the first half of 2008, but also continued well into the implementation phase. One of the new nurses attended a course at Duke University that covered screening for most of the new disorders, and afterwards presented a series of in-house training sessions to the other follow-up nurses to share this information. Follow-up nurses also attended other educational events, and were provided with written materials for self-study on the new disorders.

After surveying available options, by late 2006 the Public Health Laboratory had decided to use PerkinElmer as the primary vendor of newborn screening lab equipment, supplies, service, and related computer software. At the time, PerkinElmer was the only vendor with an FDA-approved kit for tandem mass spectrometry. Beginning around the same time, the follow-up program reviewed data systems employed in other states, and by early 2007 decided to use the PerkinElmer follow-up software package. A contract with the company was drafted during the summer of 2007, with an effective date of October 15th. Lab equipment was provided on the condition that PerkinElmer reagents were purchased, meaning that no large up-front outlay was required. However, ADH was required to pay a licensing fee for use of the software. Needed modifications to the Public Health Laboratory began in December 2007. Set-up of laboratory equipment, with training in its use and validation of results, proceeded from that point through spring of 2008. Training of lab personnel during this time occurred via on-site visits from PerkinElmer representatives.

Setting up the Public Health Laboratory's newborn screening data system encompassed a number of steps. These included configuring the demographic fields to match the state's filter paper collection card, setting up the system logic so that appropriate analytes for each disorder were measured and reported, and designing the layout and content of final results reports. After working through these and other steps, by June 2008 the laboratory was ready to go "live" with its data system. Setting up the follow-up program's notification and data software took longer, however (see "Follow-up Methodology").

As the target date for implementation approached, the need for strong interagency collaboration became increasingly acute. Two "external" subcommittees were formed in late 2007. One of these, the Medical Subcommittee, included representatives from the Arkansas Chapter of the American Academy of Pediatrics (AAP), Arkansas Academy of Family Physicians (AAFP), University of Arkansas for Medical Sciences (UAMS), Arkansas Children's Hospital (ACH), as well as ADH. This group explored the needs of primary care physicians with respect to expanded screening. As a result of these discussions, presentations were made to medical groups, including the AAP, AAFP, and Arkansas Medical Society. A mass mail-out to all primary care physicians in June 2008 described the impending expansion and included an accordion-style brochure produced by the March of Dimes. The brochure included a synopsis of each "new" disorder along with comments on potentially beneficial treatments.

The other "external" working group, the Public Awareness Subcommittee, was composed of individuals representing UAMS Department of Pediatrics, College of Nursing, and Medical Humanities; Arkansas March of Dimes; and ADH Communications, Laboratory, and Newborn Screening follow-up. Significantly, public information officers from the four largest hospitals in Little Rock were also actively involved in this subcommittee. The group worked hand-in-hand with efforts of the Arkansas Genetic Health Committee to develop key messages for dissemination to the public as part of an overall marketing plan. A press release was distributed in June 2008, and on June 24th, a major press conference was held featuring key representatives from the Department of Health, UAMS/ACH, Arkansas March of Dimes (MOD), and the Arkansas Hospital Association. The State Surgeon General and the mother of a child with a condition detected through newborn screening also spoke at the press conference. Following another recommendation by the Public Awareness Subcommittee, a toll-free number to facilitate access to program staff was established for use by parents and physicians alike. A website dedicated to newborn screening in the state, www.arnewbornscreening.com, was also established in time for the July 1st startup date. Finally, large supplies of parent brochures developed by MOD and "co-branded" by ADH were sent to every birthing hospital in the state. These brochures described the screening process and the conditions now included in the screening panel.

In addition to the external subcommittees, an internal ADH committee composed of Public Health Laboratory and Family Health Branch leaders also met. This group shared information on progress, brainstormed solutions to problems, and presented periodic updates to upper management within the Department of Health.

A major focus of activity in the final months leading up to implementation was creation of follow-up protocols for use by ADH nurse coordinators. The Department of Health

contracted with the UAMS Department of Pediatrics to draft such protocols for all of the new disorders to be screened for and to update protocols for the "old" disorders. The contract was effective as of April 1, 2008. In addition to laying out follow-up procedures on the basis of clinical rationale, the process entailed configuring the parameters of the PerkinElmer software so that the latter's logic flow matched the expected practice of the follow-up nurse. The contract also specified creation of notification (form) letters to physicians specific to each abnormal result, interpretation sheets for MD's, and fact sheets for parents. While the actual protocols, letters, interpretation sheets, and parent fact sheets were ready for use by July 1st, configuration of the more automated features of the electronic follow-up system continued well into the 2009 State Fiscal Year. Nonetheless, follow-up nurses were still able to utilize the materials generated under the contract right away. Protocols, letters, and fact sheets were reviewed periodically during the year, with necessary corrections or updates made and agreed to by both ADH and consulting staff at UAMS/ACH.

Partners

As evident from the preceding section, a number of partnerships were established to achieve the goal of expanded newborn screening in Arkansas. ADH program staff worked closely with UAMS Department of Pediatrics subspecialists both before and after implementation. The Genetics, Pulmonology, and Endocrinology Sections were all involved in recommending screening strategies, writing and reviewing follow-up protocols, and educating physicians. These professionals also provided public advocacy for expanded screening. Throughout the year, subspecialists were continuously available to program staff and primary care physicians for consultation on both individual babies and program operations as a whole.

Arkansas March of Dimes played a vital role in the expansion initiative. MOD was a strong proponent of screening from the outset, playing an integral role in education of the public and key decision-makers. The organization provided, at no cost to the program, sufficient physician brochures to reach every primary care doctor in the state. MOD also hosted the press conference held in June of 2008.

Arkansas Children's Hospital was also extremely supportive and influential in the implementation of expanded screening. ACH communications staff actively participated in public awareness efforts. Specialists from the ACH Clinical Laboratory researched, planned, and established capacity needed to provide secondary testing for Cystic Fibrosis and Congenital Adrenal Hyperplasia (see "Laboratory Screening Methodology"). And, when

no other funding source was readily identified, the hospital's leadership graciously agreed to absorb the costs of this testing.

The Arkansas Hospital Association publicly supported expanded screening, despite the large increase in fee per specimen (billed to submitter hospitals) required to make it happen. Facilitating that support was agreement by Arkansas Medicaid and major private third party payers (Arkansas Blue Cross/Blue Shield, Prudential, and others) to allow hospitals to recoup fee costs through billing for various components of the screening.

The Arkansas Genetic Health Committee worked in conjunction with the Public Awareness Subcommittee to produce key messages for the general public. The chair of the committee also produced an article on expanded newborn screening that was published in a state nursing journal.

Disorders Screened for in Arkansas

Original Disorders. Prior to July 2008, newborns in Arkansas were routinely screened for six metabolic and hematologic disorders, as well as for hearing loss. A brief description of these six disorders follows:

> *Phenylketonuria* (PKU), the very first disorder screened for in Arkansas, occurs in about one in every 15,000 births. The condition is due to lack of an enzyme that processes phenylalanine, an amino acid found in many foods. Babies with PKU may have a "musky" odor, and often show signs of irritability, abnormal reflexes, decreased pigmentation, and sometimes seizures. Left untreated, babies with PKU eventually develop severe mental retardation. If the condition is detected early enough, however, mental retardation can be completely prevented through adherence to a special diet.
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> *Congenital Hypothyroidism* (CH) occurs in about one in every 4,000 newborns. Affected babies have an underactive thyroid gland, most often caused by abnormal development of the gland. Signs and symptoms include slow mental development, along with large tongue, feeding difficulties, poor growth, constipation, prolonged neonatal jaundice, dryness of skin, umbilical hernia, edema (tissue swelling), and delayed closure of fontanels (soft spots). If recognized early enough, all of these problems -- including most importantly the delayed mental development -- can be prevented with a daily dose of oral thyroid hormone.

Sickle Hemoglobin Diseases (sickle cell anemia, sickle-hemoglobin C disease, sickle-beta thalassemia) occur in about one in every 400 African Americans. These conditions are much less common among white individuals, although they have been reported to affect those of Mediterranean heritage. The major sickling disorders are associated with abnormal red blood cells, with episodic blockage of blood vessels and so-called "pain crises." Many other complications of sickle disease also occur. Affected infants and young children are at much greater risk for certain life-threatening bacterial infections. These infections can be largely prevented through early detection and institution of prophylactic antibiotics by two months of age.

Galactosemia (GAL) is a disorder of carbohydrate metabolism that affects about one in every 40,000 newborns. The most common form is due to lack of a specific enzyme that helps break down the sugar galactose. Babies with galactosemia may experience vomiting, diarrhea, lethargy, liver disease, cataracts, and slow mental development. Behavior problems, neuropsychological deficits, and infertility are also common later in life. In the newborn period, galactosemic babies are prone to develop sepsis from certain bacteria. Early detection through newborn screening with institution of lactose-free formula is all that is needed to prevent this life-threatening complication. To lessen other complications, affected individuals are advised to avoid lactose for life.

Expanded Screening Disorders. The 22 disorders for which screening commenced on July 1, 2008 include the following:

Cystic Fibrosis (CF) occurs in about one in 3,800 individuals overall. While more common among Whites, it also affects African Americans (up to one in 15,000). CF is a complex disease affecting many parts of the body, but most prominently the respiratory system and gastrointestinal tract. Children with classic CF have difficulty clearing respiratory secretions due to production of especially thick mucus. They tend to experience many pulmonary infections, which over time often lead to permanent lung damage. Because of defects in pancreatic enzymes, many children with CF fail to absorb certain nutrients, particularly fats and fat-soluble vitamins. Therefore, they often experience poor growth. However, early detection through newborn screening with enrollment in a comprehensive treatment center has been shown to improve nutritional status and long-term growth and to decrease hospitalizations for lung infections.

Congenital Adrenal Hyperplasia (CAH) is caused by lack of an enzyme involved in the adrenal gland's production of certain hormones, such as cortisol and the salt-retaining hormone aldosterone. This disorder occurs in approximately one in 12,000 births. About 90% of cases are due to lack of an enzyme called 21-hydroxylase. When this

enzyme is missing, newborns are at risk for a so-called "salt-wasting crisis," in which excessive salt is lost in the urine and potassium is retained. Infants in such a crisis often become ill very quickly, with severe vomiting, dehydration, and lethargy, which may progress to life-threatening shock within a short period of time. Fortunately, this scenario can be averted through early detection and supplementation with appropriate hormones. Other problems associated with CAH, such as early puberty in affected males, are also less likely to occur with early treatment.

Biotinidase Deficiency (BIO) is the complete or partial absence of an enzyme involved in the body's recycling of biotin, a vitamin. Biotin is needed for effective activity of several other key enzymes. Without biotinidase, less biotin is available, ultimately resulting in such problems as developmental delay, hearing loss, poor tone, optic nerve damage, and seizures, as well as skin rash, hair loss, and conjunctivitis. Treatment with a daily biotin supplement prevents all of these problems.

New *Amino Acid Disorders* (AA) screened for include *Maple Syrup Urine Disease* (MSUD), *Homocystinuria* (HCY), *Tyrosinemia Type 1* (TYR-1), *Citrullinemia* (CIT), and *Argininosuccinic Aciduria* (ASA). Another amino acid disorder, Phenylketonuria, was described earlier. The combined incidence of these five disorders is believed to be about one in 15,000. Signs and symptoms vary by disorder, but all are due to deficiencies of enzymes that help break down amino acids found in the diet. Babies with classic MSUD usually begin having vomiting, lethargy, acidosis and a syrupy odor to the urine in the first week of life, which often progresses to coma and seizures within a short period of time. Swelling of the brain is life-threatening during this period. With HCY, infants often develop symptoms starting at several months of age, including developmental delay, dislocated lenses, and clot formation within blood vessels. The tendency to form clots in turn increases risk for stroke, seizures, and death. TYR-1 is associated with progressive liver and kidney disease beginning in the first several months of life. Affected babies grow poorly, and have acidosis, electrolyte disturbances, and a tendency to bleed freely. Finally, infants with severe CIT and ASA develop vomiting, lethargy progressing to coma, and high blood ammonia levels in the first week of life. Early recognition of all these disorders, with prompt institution of appropriate diet and medications, is absolutely necessary to prevent death and serious long-term complications.

Fatty Acid Oxidation Defects (FAO) comprise five disorders screened for: *Medium Chain Acyl-CoA Dehydrogenase Deficiency* (MCAD), *Very Long Chain Acyl-CoA Dehydrogenase Deficiency* (VLCAD), *Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency* (LCHAD), *Trifunctional Protein Deficiency* (TFP), and C*arnitine Uptake Deficiency* (CUD). The approximate combined incidence of these conditions is one in 10,000. The most

common of these, MCAD (one in 15,000 births), tends to appear in the first weeks to months of life, but may not present until years later in certain individuals. An episode of vomiting, poor tone, lethargy, low blood sugar, often progressing to coma and even death, is usually the first indication of this disorder. The other FAO defects may have similar symptoms, but also tend to involve the heart and skeletal muscles, often with permanent damage to these organs over time. Fortunately, a simple treatment exists to forestall most if not all of these problems: avoidance of fasting, sometimes in combination with a specific dietary supplement.

Organic Acidemias (OA) screened for include G*lutaric Acidemia Type I* (GA-I), *3-Hydroxy-3-Methylglutaric Acidemia* (HMG), *3-Methylcrotonyl-CoA Carboxylase Deficiency* (3-MCC), *Beta-Ketothiolase Deficiency* (BKT), M*ultiple Carboxylase Deficiency* (MCD), P*ropionic Acidemia* (PROP), M*ethylmalonic Acidemia – Mutase Deficiency* (MUT), M*ethylmalonic Acidemia – Cobal A,B Defect* (Cbl-A,B), and I*sovaleric Acidemia* (IVA). The combined incidence of these nine disorders is probably around one in 15,000. Most of the OA disorders are due to defects in enzymes that break down certain amino acids. Symptoms vary by disorder, but in general, infants with MUT, Cbl-A,B, MCD, PROP, IVA, and HMG tend to have earlier onset. These infants often show acute episodes of vomiting, lethargy, poor tone, acidosis, low blood sugar, and elevated blood ammonia. The onset of symptoms is more variable in 3-MCC and BKT, although symptoms and signs are similar to the above. In GA-I, infants often appear normal at birth, although macrocephaly (large head) may be noted in infancy. An episode of acute encephalopathy (impairment of brain function) usually develops within the first year of life, which often results in permanent neurological deficits. Alternatively, some infants with GA-I experience no "crisis," but instead show evidence of progressive developmental delay over time. For all the organic acidemias, treatment in the form of special diets and specific supplements is available.

Sample Collection

All specimens were collected on approved filter paper collection forms issued by the Department of Health. Collection of a satisfactory sample generally entailed pricking the infant's heel, and allowing the blood to drop onto the collection card until all of the outlined circles were filled. After collection, specimens were sent to the Public Health Laboratory in Little Rock for processing and analysis. Providers who submitted specimens (most commonly, hospitals) were expected to adhere to applicable Rules and Regulations regarding timing and submission of specimens.

The filter paper collection card was revised during the year to reflect the expanded screening. Certain new data fields were added, and others deleted or modified. However, no additional blood was required to perform screening for the new disorders.

To promote quality of filter paper specimens and timeliness of their submission, ADH hired a newborn screening outreach nurse in December, 2007. Hospitals with the highest numbers of births were targeted for initial visits, with provision of in-service training for nursery personnel and other staff involved in sample collection. The outreach nurse also obtained data from the newborn screening laboratory on hospital-specific specimen rejection rates, and utilized this information during site visits. Between April and October of 2008, the outreach nurse managed at least one visit to every hospital in the state that delivered babies. Additional visits later in the reporting year were conducted as needed.

Laboratory Screening Methodology

The Arkansas Department of Health (ADH) Public Health Laboratory served as the primary site for newborn screening laboratory activities. As mentioned previously, much work was required to obtain the necessary equipment for expanded screening and become proficient in its use. Implementation of screening using tandem mass spectrometry posed particular challenges. In addition to the aforementioned on-site, startup training provided by PerkinElmer, during the reporting year key lab personnel attended trainings at both the Mayo Clinic and Baylor University on use of tandem mass spectrometry. Expansion also entailed a switch from an antiquated Wang mainframe to a new PC-based data system. This transition officially occurred in July 2008, when expanded screening began.

To minimize false positive results for two of the screened disorders, Cystic Fibrosis and Congenital Adrenal Hyperplasia, experts within the state determined that secondary testing of positives using more specific assays was advisable. Since this decision was not finalized until well after the fee increase had been approved, no funds were budgeted for this testing. During the first three months of expanded screening, specimens needing secondary tests for CAH were sent to the Mayo Clinic, which charged a modest fee for each specimen analyzed. Fortunately, Arkansas Children's Hospital (ACH) generously agreed to perform secondary testing for CF beginning in July 2008, and for CAH starting in October 2008, at no charge to the program. This arrangement was later formalized in a Memorandum of Agreement between ADH and ACH.

The Public Health Laboratory contracted with PerkinElmer, one of the nation's largest vendors of newborn screening systems, to provide the equipment and technical support necessary to expand the screening panel. The company helped to train laboratory

personnel in use of new equipment and kits, and also configured the laboratory data system to meet the unique needs of the Department of Health.

A summary of newborn screening strategies and methods employed for each disorder or group of disorders follows.

Congenital Hypothyroidism
Thyroid stimulating hormone (TSH) levels were measured in all specimens by fluorometric immunoassay. For those in whom the TSH level fell in the upper 10% of the day's run, a thyroxine (T4) level was also measured by similar methodology. However, the TSH value was the primary determinant of whether the screen was designated "normal" or "abnormal."

Sickle Hemoglobin Diseases
High phase liquid chromatography (HPLC) was employed for all specimens. Isoelectric focusing was used as a secondary method to further delineate and "confirm" initial positive results.

Galactosemia
Quantitative (fluorometric) measurement of galactose-1-phosphate uridyl transferase (GALT) enzyme activity

Cystic Fibrosis
First tier screening was carried out through quantitative measurement of immunoreactive trypsinogen (IRT). Specimens in the top 2% of the week's IRT values were sent to Arkansas Children's Hospital for CF gene mutation analysis (46 mutation panel).

Congenital Adrenal Hyperplasia
First tier screening was conducted through quantitative measurement of 17-hydroxyprogesterone (17-OHP) via fluorometric immunoassay. Specimens exceeding cutoff values were sent to Arkansas Children's Hospital for steroid profile testing, using liquid chromatography–tandem mass spectrometry.

Biotinidase Deficiency
Colorimetric/qualitative enzyme assay

Amino Acid Disorders (Including PKU)
Tandem mass spectrometry

Fatty Acid Oxidation Defects
Tandem mass spectrometry

Organic Acidemias
Tandem mass spectrometry

Follow-up Methodology

As mentioned earlier, written protocols for follow-up of every possible abnormal screening result were meticulously crafted and approved through metabolic specialists at UAMS/ACH. While different for each disorder/result, all the protocols attempted to assure a high level of safety for infants with positive results, while also minimizing additional recommended laboratory tests or procedures for infants whose results suggested a low likelihood of disease. For example, for most infants with "borderline" results on tandem mass spectrometry, a repeat filter paper specimen was requested, rather than comprehensive metabolic diagnostic testing. For such infants at relatively low risk for disease, this approach minimized costs while still assuring absence of disease.

Follow-up nurses hired into the Newborn Screening Program before and during the first year of expanded screening received extensive training in the conditions screened for, as well as in use of follow-up protocols for abnormal results. Several of the nurses attended out-of-state seminars related to expanded screening. Local and in-house opportunities for NBS education were also made available to follow-up nurses.

As a general rule, positive results were phoned and faxed to affected infants' primary care physicians. A later mailing of final results through the postal service also occurred. At the time of the initial notification, MD interpretive materials and information sheets for parents were also routinely faxed to physicians' offices. These materials explained the significance of the particular abnormal screening result, and provided physicians with written recommendations on specific tests or procedures to perform to confirm or rule out the disorder in question. These materials were largely developed under contract with the UAMS Department of Pediatrics (Genetics Section). For CF and CAH screening, only positive secondary tests were reported to physicians, <u>not</u> the initial positive ("first tier") results. Negative secondary tests for these disorders were reported in writing to the submitting hospitals.

In cases in which the physician listed on the newborn screening form was not seeing the infant following hospital discharge, the follow-up nurses worked to ascertain the identity of

the baby's current physician. In some cases, this involved contacting the parent of the baby directly. As a rule, however, parents were not notified directly of abnormal screening results.

Protocols for the ADH follow-up nurses spelled out when to re-contact primary care physicians' offices to assess status of confirmatory testing efforts. If needed, screening reports and interpretive materials were re-faxed to the provider's office, followed by repeat contacts with the doctor's office. In cases in which the MD was unable to reach the parent, follow-up nurses made use of other databases to attempt to locate the family, such as WIC and the Immunization Registry. If called for by the situation, the follow-up nurses attempted direct contact with families through phone calls and registered letters. County health units were also sometimes contacted directly to see if the family had come in recently for any other services. In general, follow-up protocols were written to ensure that follow-up efforts proceeded until the disorder in question was either confirmed or excluded.

To expedite follow-up for infants needing confirmatory testing and/or subspecialty care, in July 2008 a Newborn Screening Coordinator position was established under contract with the UAMS Department of Pediatrics. This position, filled by a genetic counselor, was instrumental in coordinating activities between ADH and ACH in a number of areas. For example, the UAMS/ACH coordinator communicated secondary test results for CF and CAH (performed in the ACH Laboratory), served as a liaison between ADH personnel and ACH pediatric subspecialists, assumed primary responsibility for arranging sweat tests for babies with abnormal CF screening results, and helped arrange appointments to ACH for babies needing either diagnostic testing or subspecialty care.

Yet another asset to follow-up activities was the creation of a Newborn Screening Clinic at ACH during the summer of 2008. This clinic operated in conjunction with the General Pediatric Clinic (GPC), and served as a site for primary care physicians to refer infants needing confirmatory testing. The clinic was structured so that babies could be seen almost immediately, and relevant subspecialists would either be available to see the infant personally, or to consult by phone with GPC physicians.

Prior to expansion, the follow-up program used traditional paper records to track infants with positive screens. As mentioned under "Implementation Activities," in SFY08 the program researched potential vendors for an electronic follow-up system, and settled on the PerkinElmer Patient Care package. This system was chosen in part due to its seamless interface with the laboratory data system. The software allowed for virtually automatic generation of letters to physicians specific to an individual infant's abnormal screening result. It also generated up-to-the-minute lists of abnormal results by category of disorder

(i.e. results requiring nurse action). Follow-up nurses were able to chart notes in the system just as they would a paper record, and also to scan in diagnostic laboratory results from "outside" sources. The system was phased in over the course of the first year of expanded screening, with a validation phase from October 2008 through March 2009. The system went fully "live" April 1, 2009, resulting in significantly less paper charting.

To facilitate coordination of follow-up, a link to the Patient Care data system was installed on the UAMS/ACH Newborn Screening Coordinator's computer. This link enabled the remote Coordinator to access abnormal results. Additionally, a shared Access database was established to expedite medical consultation on screening results for some of the more time-sensitive disorders. These electronic connections were established and secured by ADH Information Systems personnel. Arrangements for information-sharing were formalized through contract with the UAMS Department of Pediatrics, which included a HIPAA Business Associates Agreement.

The follow-up nurses were backed up by the Program Medical Director, who was always available for consultation. Subspecialists in the UAMS Department of Pediatrics were also under contract to provide consultation on positive results, as well as on overall quality improvement issues. Given the relative rarity of most of the conditions screened for, and the highly technical nature of the screening process, input from these specialists on a regular basis was deemed essential.

Results

Completeness of Screening

A data matching program to link birth records with newborn screening results was developed through the ADH Center for Health Statistics. The match process involved 9 demographic variables, with 42 possible combinations considered a "match." For the reporting year, 38,750 births occurred within Arkansas's borders, of which a matching newborn screening record was found for 38,172. These figures imply that 98.5% of infants born in the state had a newborn screening specimen submitted.

Results by Disorder/Category

A summary of screening results for each disorder or category of disorder follows. These results pertain to specimens received in the ADH Public Health Laboratory between July 1, 2008, and June 30, 2009. Note that results for Phenylketonuria (PKU) are included under the Amino Acid Disorders category. Screening for PKU was carried out using tandem mass spectrometry during the reporting period.

Note: All of the following "% of total" figures are based on a total of 38,172 initial screens.

Congenital Hypothyroidism

Initial positives* (% of total)	994	(2.6)
Confirmatory/repeat test normal	970	
Lost to follow-up, before confirmatory test	3	
Confirmed cases	21	
Confirmed cases who received treatment (%)	21	(100)
Confirmed cases lost to follow-up (%)	0	(0)

*266 (27%) of the initial positives were from specimens collected prior to 24 hours of age. Too-early specimen collection is strongly associated with false-positive results for congenital hypothyroidism. None of the confirmed cases came from specimens collected too early.

Sickle Hemoglobin Diseases

Sickle Cell Anemia, Sickle-β^0-Thalassemia (FS results)

Initial positives (% of total)	12	(0.03)
Confirmatory test normal	0	
Lost to follow-up, before confirmatory test	0	
Confirmed cases	12	
Confirmed cases who received treatment (%)	12	(100)
Confirmed cases lost to follow-up (%)	0	(0)

Sickle-Hemoglobin C Disease (FSC, FCS results)

Initial positives (% of total)	12	(0.03)
Confirmatory test normal	0	
Lost to follow-up, before confirmatory test	0	
Confirmed cases	12	
Confirmed cases who received treatment (%)	12	(100)
Confirmed cases lost to follow-up (%)	0	(0)

Sickle-β^+-thalassemia (FSA results)

Initial positives (% of total)	1	(0.003)
Confirmatory test normal	0	
Lost to follow-up, before confirmatory test	0	
Confirmed cases	1	
Confirmed cases who received treatment (%)	1	(100)
Confirmed cases lost to follow-up (%)	0	(0)

Galactosemia

Initial positives (% of total)	214 (0.6)
Confirmatory test normal	211
Lost to follow-up, before confirmatory test	0
Physician inaction	2
Parental refusal	1
Confirmed cases – classic galactosemia	0
Confirmed cases – variant galactosemia	20
Confirmed cases who received treatment (%)	20 (100)
Confirmed cases lost to follow-up (%)	0 (0)

Cystic Fibrosis

Initial positives - first tier screening (% of total)	785 (2.0)
Positive mutation analyses - second tier screening (% of total)	78 (0.2)
Confirmatory (sweat) test normal	68
Lost to follow-up, before confirmatory test	0
Confirmed cases	10
Confirmed cases who received treatment (%)	10 (100)
Confirmed cases lost to follow-up (%)	0 (0)

Congenital Adrenal Hyperplasia

Initial positives - first tier screening (% of total)	826 (2.2)
Positive steroid profiles - second tier testing (% of total)	17 (0.04)
Confirmatory test normal	14
Lost to follow-up, before confirmatory test	0
Confirmed cases	3
Confirmed cases who received treatment (%)	3 (100)
Confirmed cases lost to follow-up (%)	0 (0)

Biotinidase Deficiency

Initial positives (% of total)	7 (0.02)
Confirmatory test normal	6
Lost to follow-up, before confirmatory test	0
Confirmed cases	1
Confirmed cases who received treatment (%)	1 (100)
Confirmed cases lost to follow-up (%)	0 (0)

Amino Acid Disorders

Initial positives* (% of total)	333 (0.9)
Confirmatory/repeat test normal	324
Lost to follow-up, before confirmatory test	4
Physician inaction	2
Confirmed cases**	4
Confirmed cases who received treatment (%)	4 (100)
Confirmed cases lost to follow-up (%)	0 (0)

*Specimens displaying more than one amino acid abnormality were counted as a single positive result

**3 cases of Phenylketonuria, 1 case of Citrullinemia

Fatty Acid Oxidation Defects

Initial positives* (% of total)	37 (0.1)
Confirmatory/repeat test normal	32
Lost to follow-up, before confirmatory test	1
Deceased, before confirmatory test**	1
Confirmed cases***	3
Confirmed cases who received treatment (%)	3 (100)
Confirmed cases lost to follow-up (%)	0 (0)

* Specimens displaying more than one screening abnormality suggestive of fatty acid oxidation defect were counted as a single positive result

** One neonate with results highly suggestive of Medium Chain Acyl-CoA Dehydrogenase Deficiency died of unrelated causes prior to confirmation

*** 2 cases of Medium Chain Acyl-CoA Dehydrogenase Deficiency, 1 case of Very Long Chain Acyl-CoA Dehydrogenase Deficiency

Organic Acidemias

Initial positives* (% of total)	153	(0.4)
Confirmatory/repeat test normal	148	
Lost to follow-up, before confirmatory test	3	
Physician inaction	1	
Parental refusal	1	
Confirmed cases	0	
Confirmed cases who received treatment (%)	0	(0)
Confirmed cases lost to follow-up (%)	0	(0)

* Specimens displaying more than one screening abnormality suggestive of organic acidemia were counted as a single positive result

Discussion

Significance of Results

Because the conditions screened for are relatively rare, results of screening from a single year are somewhat inconclusive and do not permit accurate calculation of incidence of the various disorders in Arkansas. For example, the lack of detected cases of organic acidemia in the first year is insufficient evidence on which to conclude that these disorders are not present in Arkansas. These conditions will in fact be detected in future years of screening. For some such conditions, five years or more of screening experience may be required in order to estimate the true incidence in Arkansas.

In general terms, however, results of screening in Arkansas matched expectations based on incidence figures reported nationally and from other large state screening programs. For example, about 10 new cases of Cystic Fibrosis would be expected in Arkansas each year, and 10 were detected. About 4 fatty acid oxidation defects would be expected each year; 3 were confirmed, and another was highly probable based upon screening results. Results for Congenital Adrenal Hyperplasia were also exactly as predicted, with 3 cases found. With the possible exception of organic acidemias, screening for other disorders also matched or exceeded expected results.

An extremely small number of infants were lost to follow-up after positive screening results, reflecting a high level of diligence on the part of follow-up staff. In these rare instances, families could not be reached even after multiple attempts by physicians' offices and program staff. Likewise, in very few cases did physicians or parents refuse to comply with requested follow-up testing. Significantly, no infants were lost to follow-up <u>after</u>

confirmation of disease; the program assured that all such infants were under the care of an appropriate provider.

For the most part, rates of positive screens for the various "new" disorders were approximately as anticipated. Secondary screening methods for Cystic Fibrosis (CF) and Congenital Adrenal Hyperplasia (CAH) were exceedingly effective in minimizing positive results reported to physicians. Only 0.2% of infants had positive CF results reported, while only 0.04% had positive CAH results reported. The positive rate for Biotinidase Deficiency screening was also extremely low, at only 0.02%. Positive rates for organic acidemias (0.4%) and fatty acid oxidation defects (0.09%) were reasonable, but the rate of positivity for amino acid disorders (0.84%) was higher than expected. Many of the positives for amino acid disorders, and to a lesser extent those for organic acidemias, occurred in association with administration of total parenteral nutrition (TPN) to the infants. TPN, which involves giving nutrients intravenously rather than through the gastrointestinal tract, is well-known to produce false positives on tandem mass spectrometry screening. Approximately 50% of the amino acid positives during the reporting year were linked to TPN, all of which were false positives. Nonetheless, positive results from infants receiving TPN must always be pursued, as metabolic disease in such infants is still possible.

A Few Lessons

Those deeply involved in implementation of expanded newborn screening in Arkansas perceived several key aspects critical to success. First, in all phases from planning through full implementation, a collaborative approach was essential. The complexity of expanded screening demanded that public health, vendors, medical consultants, hospitals, communications staff, advocacy groups, third party payers and others all work together in a coordinated fashion to reach a common goal.

Second, the need for appropriate communication among all elements of the newborn screening system was strongly reinforced during expansion. For example, the Public Health Laboratory had to rapidly report positive results to follow-up personnel, who in turn had to promptly communicate these to physicians along with appropriate interpretive information. To facilitate this communication, an electronic follow-up system was chosen which allowed for abnormal results to appear in the follow-up program's software as soon as tests were finalized by the Public Health Laboratory. Although the follow-up system did create certain efficiencies, it did not result in a "paperless" record altogether. Paper materials still had to be printed and faxed to physicians, and paper reports of confirmatory testing still had to be faxed by physicians' offices and then scanned into the follow-up system to complete an electronic record. Physicians also had no direct electronic access to results of screening on a given infant. While on the whole, information still flowed

promptly, improved data transfer between appropriate entities - which still safeguards the privacy of infants and families - remains a high priority.

Current and Future Directions

The program is currently engaged in active exploration of strategies to reduce false positive results, particularly those produced by tandem mass spectrometry (MS/MS) screening. For example, since levels of certain amino acids have been observed to increase over the first few weeks of life, age-specific cutoffs may be developed. Secondary analytes and ratios utilized in MS/MS screening may also be modified to produce more specific screening results. Finally, a few cutoffs for initial analytes may also be adjusted. Such changes in screening methodology require careful consideration to avoid any risk of missing affected infants.

On a broader scale, the program is continuing efforts to make the public aware of newborn screening and its potential benefits. The program website is being updated to include more information and helpful links for both families and physicians. Condition-specific information sheets for parents and physicians have recently been reviewed and updated. A newborn screening subcommittee of the Arkansas Genetic Health Committee has recently been formed to assist in quality improvement activities and consider future expansions in screening.

A few years of screening may be required before it is possible to fully evaluate the impact of the expansion in terms of cost savings. The UAMS Department of Pediatrics – Genetics Section has recently received a grant from Arkansas Medicaid which provides sufficient funds for such an evaluation plus assessment of key process-based quality measures. The grant, which is potentially annually renewable, also will cover the costs of (1) secondary testing for CF and CAH, (2) metabolic foods and formulas for affected individuals, and (3) further development of information systems infrastructure. Personnel to provide longer follow-up of confirmed cases than previously possible may also materialize as a result of the grant.

Looking farther down the road, new candidate conditions for newborn screening are continually being proposed. Program personnel and the many partners still engaged in current efforts maintain a high level of vigilance for such conditions and will recommend appropriate additional screening when the time is right to expand again.